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Formalizing the mechanism of the allylic substitution reaction (S_N'): application to the highly enantio- and diastereo-selective syntheses of 1-phenyl-2-vinylcyclopentanes

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***In memoriam* Prof. Gilbert Stork, a superb and dedicated scientist, who discovered, amongst many other reactions, the stereochemical outcomes of the S_N' reaction**

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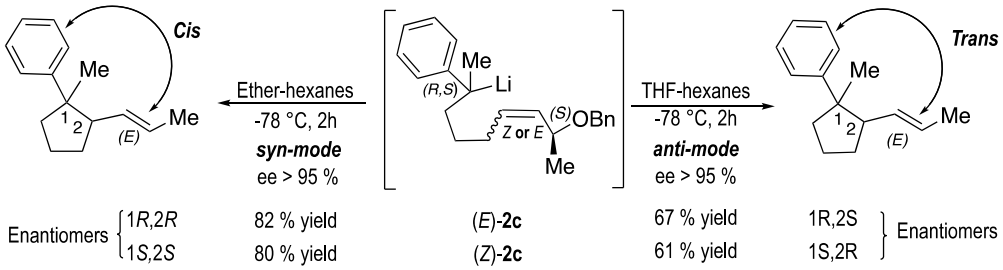
Abstract

We report efficient stereoselective and high yielding syntheses of each of the four enantiomers of phenylcyclopentanes bearing a quaternary center and a *E*-propenyl chain on the adjacent carbon that involves intramolecular allylic substitution reactions. In complement to its synthetic value, this process models the S_N' reaction and allows prediction of its stereochemical outcome.



Keywords: Benzyl selenides, Se/Li exchange, stereospecific carbocyclization, aryl cyclopentanes, $S_{N'}$ reaction

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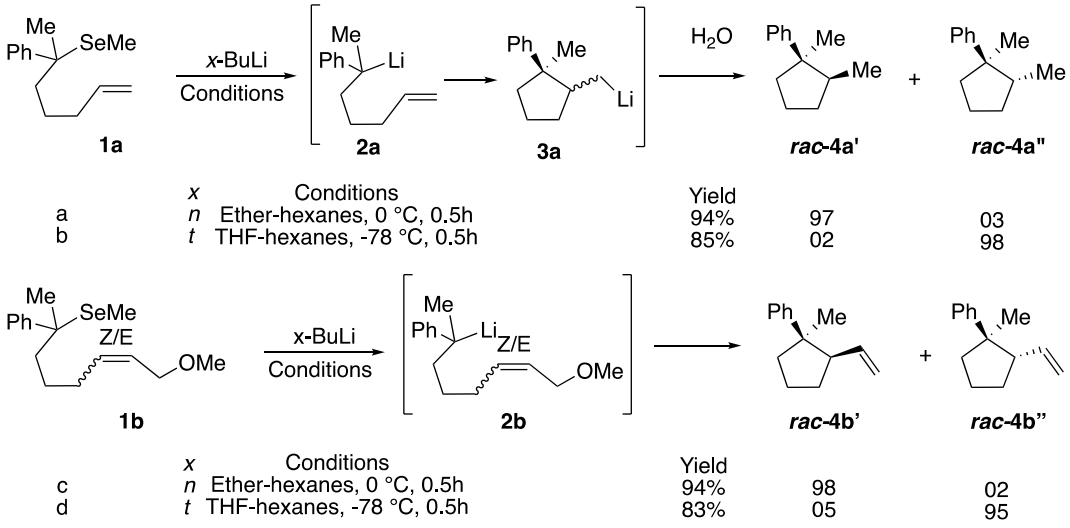
Introduction

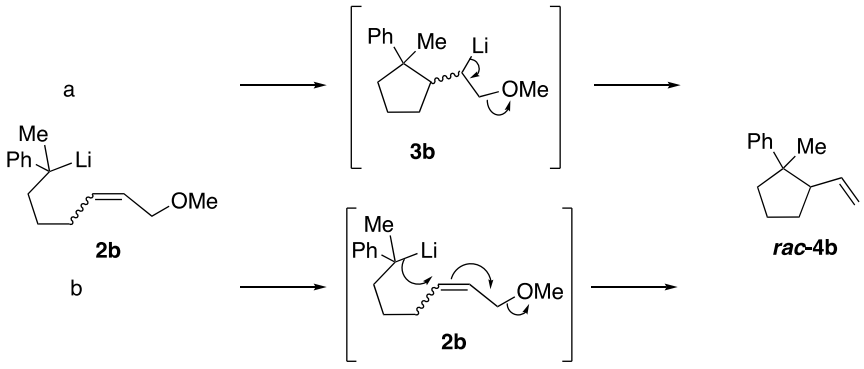
Several years ago we described a high yielding synthesis of cyclopentane derivatives **4a** bearing a benzylic quaternary center and substituted on the adjacent carbon by a methyl group, from benzylselenide **1a** bearing a CC double bond four carbons away from the benzylic carbon.[1,2] It involved the intermediate formation of the related benzyllithium, its *exo-trig* addition[3] across the built-in CC double bond, and protonation of the resulting cyclopentylmethyllithiums **3a** (Scheme 1, entries a,b).

Interestingly, we found that this carbocyclization reaction occurs with high stereocontrol that depends upon the solvent and the temperature used.[1] It leads to the stereoisomer *rac*-**4a'** in which the phenyl group and methyl group on the adjacent carbons are *cis* when the reaction is carried out in pentane or diethyl ether-hexanes between -20 and 20 °C and to *rac*-**4a"** in which the same substituents are *trans* when the reaction is instead carried out in THF-hexanes at -78 °C.[1]

We later observed similar stereochemical features from benzylselenides **1b** possessing either a *Z*- or *E*-allylic ether moiety (Scheme 1, entries c,d),[2,4] but were unable to determine whether the process that involves the intermediate formation of benzyllithiums (Scheme 1, entries c,d) occurs through a stepwise (Scheme 2, entry a) or a concerted allylic substitution reaction (Scheme 2, entry b).



Scheme 1



Scheme 2

We decided to carry out on **1c**, the higher homologs of **1b**, the reactions shown in Scheme 1, being aware that the presence of an extra methyl group on the allylic carbon on **1c** will imply an extra stereochemical

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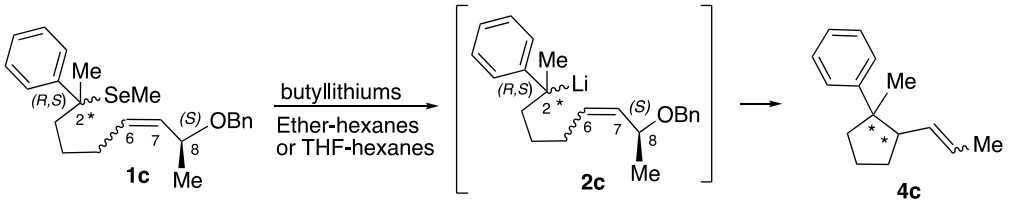
center at C-8 in addition to the existing ones, namely the benzylic C-2 carbon and the Δ^{6-7} CC double bond (Scheme 3). We expected to be able to (i) generate *on demand* five-membered ring carbocycles with high absolute and relative stereocontrol, (ii) gain at the same time insight into the intimate mechanism of such process, and ultimately (iii) propose a model to predict the stereochemical outcome of any allylic substitution reaction (S_N' reaction).



Scheme 3

Since this reaction involves an intramolecular process, It was expected to favor the allylic substitution reaction (S_N') at the expense of the competing substitution reaction (S_N), that is beneficial for the interpretation of the experiments and for the synthetic value of the process.

The S_N' reaction has been the subject of very much experimental and theoretical work over the last 60 years,[5-10] that attests the significance attached to the phenomenon.[8] This reaction can deliver up to four stereoisomeric products possessing either a *Z*-CC double bond (Figure 1, $\mathbf{S_Z}$, $\mathbf{A_Z}$) or *E*-CC double bond (Figure 1, $\mathbf{S_E}$, $\mathbf{A_E}$) from a single stereoisomer of the allylic electrophile, with a net preference for the formation of the latter products possessing *E*-CC double bonds. Those products formally result from the attack, on each of the two remarkable conformers of the starting material, of a nucleophile entering from the same face of the CC double bond than the departing group (*syn*-mode; Figure 1, $\mathbf{S_Z}$, $\mathbf{S_E}$) or from its opposite face (*anti*-mode; Figure 1, $\mathbf{A_Z}$, $\mathbf{A_E}$).

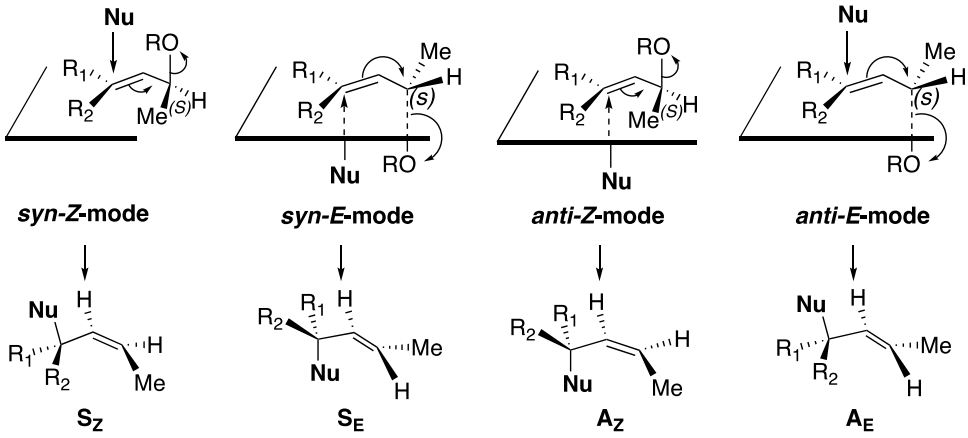


Figure 1

Surprisingly, although a great many experiments have been carried out on a wide variety of starting materials[5-9] involving charged and uncharged nucleophiles, different families of leaving groups and experimental conditions that include metal-catalyzed processes,[11,12] over a long period, only rare systematic studies have been carried out and up to now it has been impossible to predict with confidence the stereochemical outcome of any S_N' reaction.

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The transcript[13] of a part of an interview, still of highly topical interest, with the late Prof. Gilbert Stork, who provided seminal contributions[5-9,11,14-18] to the mechanism of the SN' reaction, sheds a proper light on this process: "*That was good and bad. It turned out to be sort of the wrong kind of reaction to get involved with. It was intriguing at the time. It turned out to be (i) enormously more complicated than anyone knows; even today no one understands it, and (ii) not important. It became a known piece of work because there were not that many qualitative mechanistic studies at that time"*.

We selected as starting materials unsaturated benzylselenides **1c** bearing a benzyloxy group at their allylic carbon atoms possessing all the fixed 8(*S*) stereochemistry and either *Z*- (**1c$_Z$**) or *E*- (**1c$_E$**) Δ^{6-7} CC double bonds. We decided for convenience, to carry out the reactions on mixtures of the two epimeric selenides possessing the [2(*R*) and 2(*S*)] configuration at their benzylic carbons, expecting that it would circumvent inherent synthetic difficulties and will not interfere with the cyclization reaction due to the well-known ease by which benzyllithium intermediates interconvert.[19,20]

We expected that the process would initiate a series of asymmetric inductions from the allylic (*S*)-C-8 carbon that would allow to control the stereochemistry at each newly created asymmetric centers depending upon the nature of the solvent (Ether or THF) and therefore to produce from each of the two couples [2(*R*) and 2(*S*)] of stereoisomers [**1c$_Z$** or **1c$_E$**] a major product different from the others.

The strategy developed for the synthesis of each of the two epimeric mixtures of starting materials **1c$_E$** and **1c$_Z$** disclosed in Figure 2 is commented upon here. Their synthesis along with the related experimental part is presented below. The strategy involves the selection of:

1. commercially available[21] scalemic (*S*)-3-butyn-2-ol (**5**) able to deliver to **1c** a four carbon unit (C-6 to C-9) with an hydroxyl group on a (*S*)-(C-8) carbon atom and carrying a terminal CC triple bond possessing the aptitude to be (i) easily metallated and alkylated at its *sp* carbon, after protection of its hydroxyl group and (ii) stereoselectively reduced to a disubstituted CC double bond (Δ^{6-7} CC double bond) possessing either the (*Z*) or the (*E*) stereochemistry, using respectively either the Lindlar catalyst[22] that finally leads to **1c$_Z$** (Figure 2, entry a), or Red-Al[23] that takes advantage of its hydroxyl directed hydroalumination, leading finally to **1c$_E$** (Figure 2, entry b),
2. 2,2-bis(methylseleno)ethylbenzene, readily available[2,24] from acetophenone and methylselenol, is the precursor of the 1-lithio-1-ethyl-1-methylseleno-benzene[2,25] expected to bring the two-carbon unit of the chain (C-1 and C2) and the benzylic carbon (C-2) flanked with the methylseleno moiety, potential precursor of the corresponding benzyllithium **2c** (Figure 2). Both benzyllithiums are prone to be alkylated by alkyl halides (by substitution) or CC double bonds (by addition),[2]
3. complementary compounds bearing three carbon straight chain (C-3,C-5) that possess different leaving groups at each of their termini to allow selective sequential alkylations with the functionalized acetylide and then with the 1-lithio-1-ethyl-1-(methylseleno)benzene.

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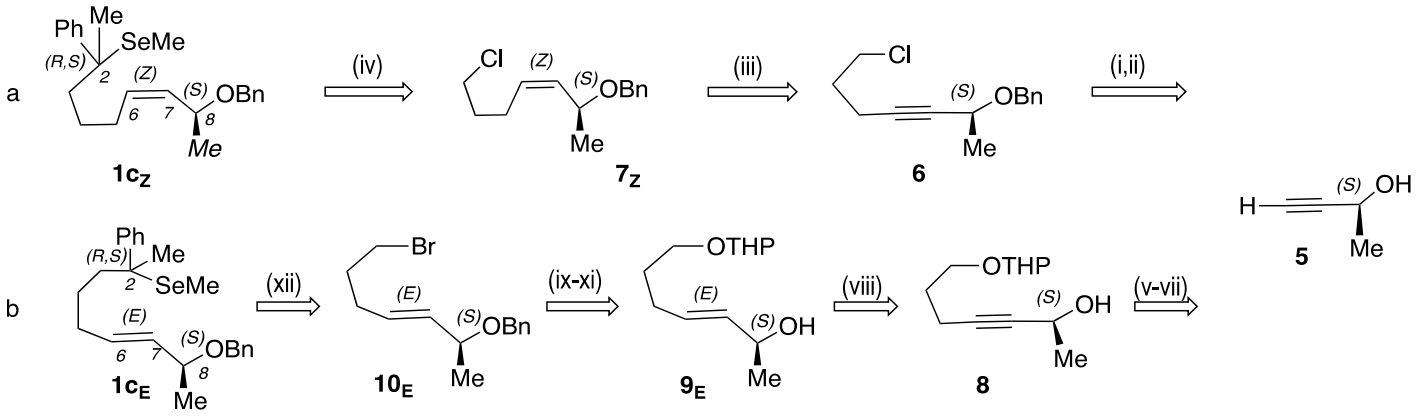

(i) $PhCH_2Br$/Base (ii) Base/$Br(CH_2)_3Cl$ (iii) H_2/Lindlar catalyst/quinoleine (iv) PhCMeLi(SeMe) (v) Base/TBDMSCl (vi) Base/$Br(CH_2)_3OTHP$ (vii) F^- (viii) (a) Red-Al (b) H_2O (ix) Base/BnBr (x) H^+ (xi) CBr_4/PPh_3,(xii) PhCMeLi(SeMe).

Figure 2

Results and Discussion

Experimental results

We have systematically carried out the reactions between epimeric mixtures of benzyl selenides **1c$_Z$** and **1c$_E$** and butyllithiums at -78 °C using diethyl ether-hexanes (Scheme 4, entries a,c) or THF-hexanes (Scheme 4, entries b,d) as solvents. As previously observed, the cleavage of their CSe bond is efficiently achieved by *n*-BuLi in THF-hexanes, whereas it requires the more reactive *t*-BuLi if ether-hexanes is instead used (Scheme 4, entries a,c).

Each of those reactions led in reasonably high yields (65-88 %) to a stereoisomeric mixture of 1-phenyl-2-propenylcyclopentane derivatives **4c** in which the one possessing the *E*-CC double bond largely prevails (100-93 %, Scheme 4).

(i) The stereochemistry of the major products (**4c$_{E1}$**- **4c$_{E4}$**, Scheme 4) was found to be dependent both the nature of the solvent used and on the stereochemistry of the starting materials **1c**. In accordance with our previous results (Schemes 1), those (**4c$_{E1}$** and **4c$_{E3}$**, Scheme 4, entries a,c) resulting from the reactions carried out in ether-hexanes possess a *cis*-relationship between the phenyl and the propenyl groups and are produced through the *syn*-*E*-mode (Scheme 4, entry a) whereas those (**4c$_{E2}$** and **4c$_{E4}$**) generated in THF-hexane possess a *trans*-relationship between the same groups and their formation instead involve the *anti*-*E*-mode (Scheme 4, entries b,d).

Each pairs of products **4c$_{E1}$** and **4c$_{E3}$** (Scheme 4, compare entry a with c) and **4c$_{E2}$** and **4c$_{E4}$** (Scheme 4, compare entry b with d), generated from different starting materials but in the same solvents, are enantiomers. Whereas each pair of products **4c$_{E1}$** and **4c$_{E2}$** (Scheme 4, compare entry a with b) and **4c$_{E3}$** and **4c$_{E4}$** (Scheme 4, compare entry c with d) generated from the same starting material but in different solvents are diastereoisomers with cyclopentane rings on which the carbons bearing the phenyl ring possess the same stereochemistry, and consequently the ones to which is attached the propenyl side chain bears an inverted stereochemistry.

(ii) The stereochemistry of the minor products (**4c$_{E3}$**, **4c$_{Z1}$**, and **4c$_{E1}$**, Scheme 4, entries b-d) that are formed in less that 7% besides almost all the major products (**4c$_{E2}$**-**4c$_{E4}$**, Scheme 4, entries b-d, except Scheme 4, entry a) also depends on the stereochemistry of the starting material and the solvent. They all

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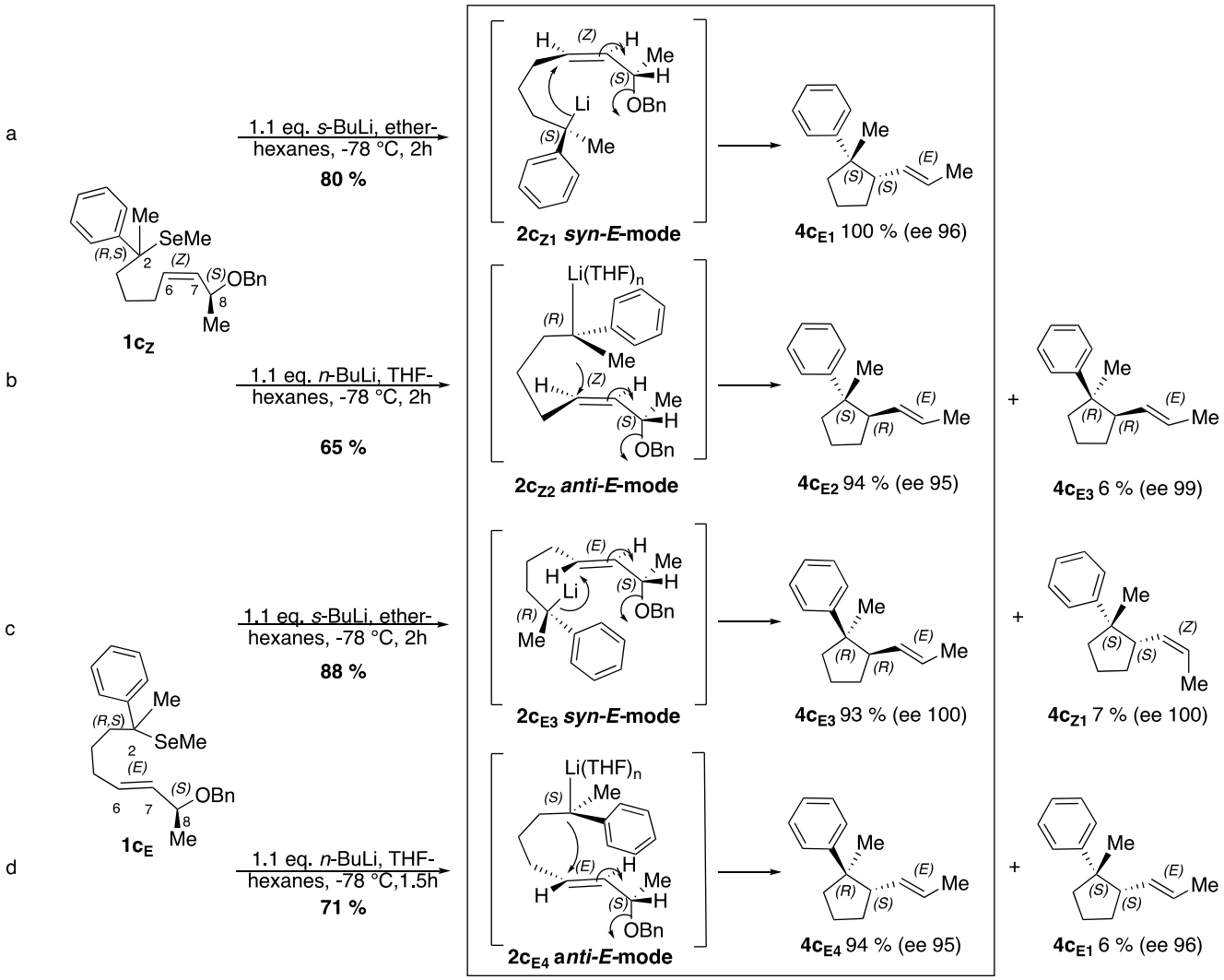
nevertheless exhibit a *cis*-relationship on the cyclopentane ring between the phenyl and propenyl groups and possess all a benzylic carbon that is epimeric to that of the related major stereoisomer. The minor stereoisomer **4c$_{Z1}$** (Scheme 4, entry c) is the only product that possesses a *Z*-CC double bond. Interestingly its formation as the one of the major stereoisomer **4c$_{E3}$** involves the *syn*-mode (although it is the *syn*-*Z*-mode instead of the *syn*-*E*-mode; Scheme 4, entry c).



Scheme 4

We have also observed in the tandem Se/Li exchange-carbocyclisation reactions carried at 0 °C instead of -78 °C that the amount of the minor isomer always increases at the expanse of the major product (Schemes 5). This is particularly the case of reactions performed in THF-hexanes (Schemes 5, entries b,d). It still affects the reaction of **1c$_{Z1}$** that delivers in ether-hexanes compound **4c$_{Z1}$**, possessing a *Z*-propenyl side chain in quite high yield (30 %, Scheme 5B, entry c) but does not affect the outcome of the reaction involving its *E*-stereoisomer **1c$_{E1}$**, performed in the same mixture of solvents (Scheme 5A, entry a).

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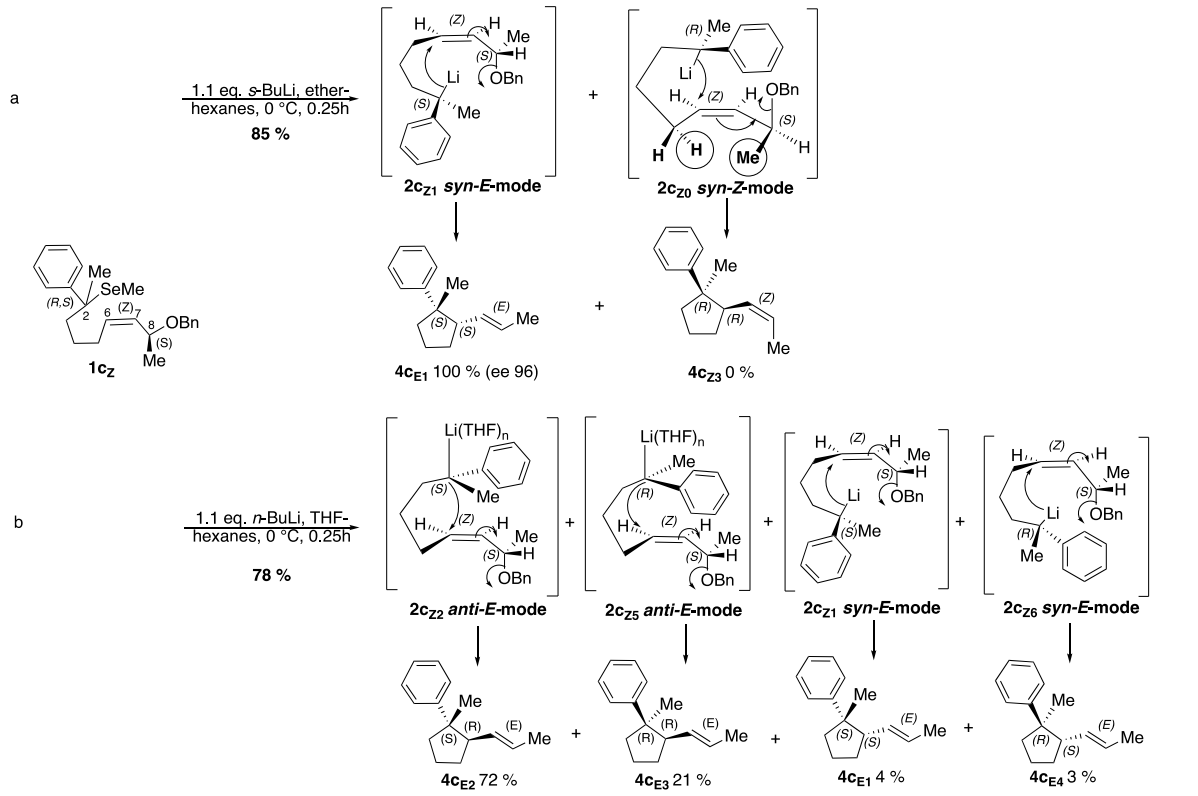
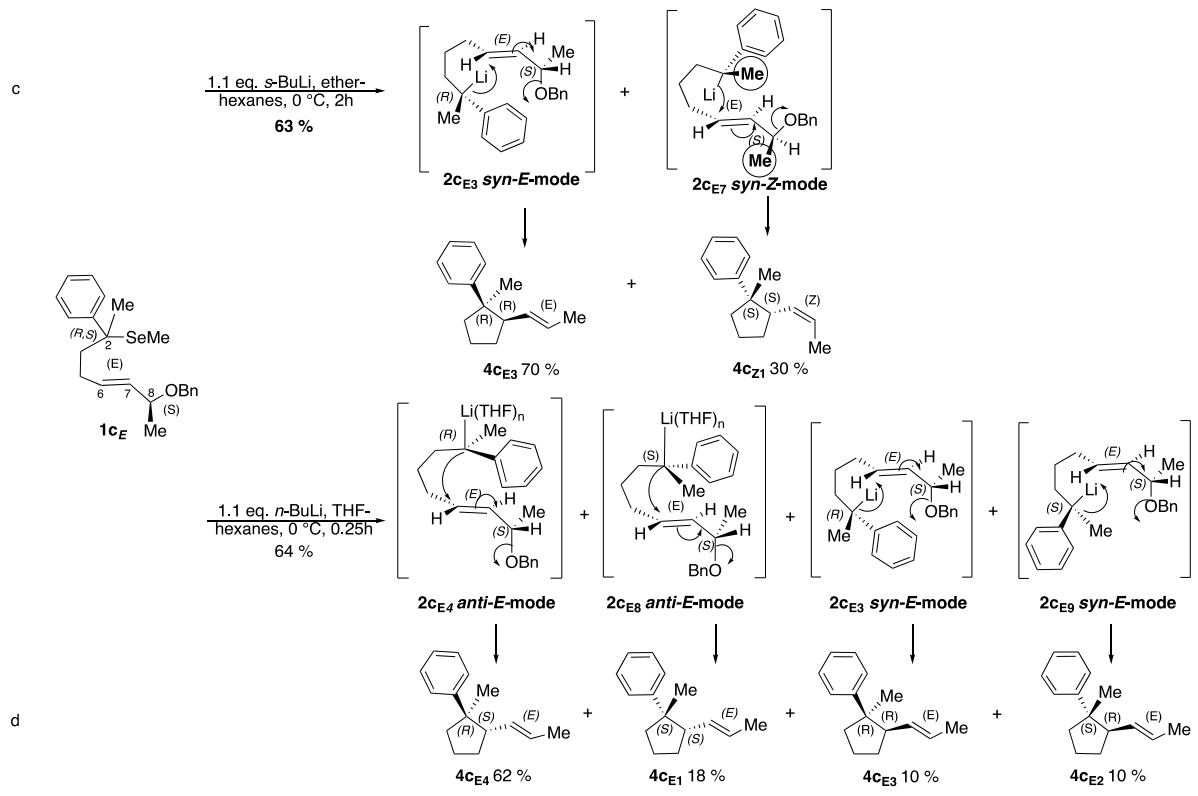


Scheme 5A



Scheme 5B

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Interpretation of the results

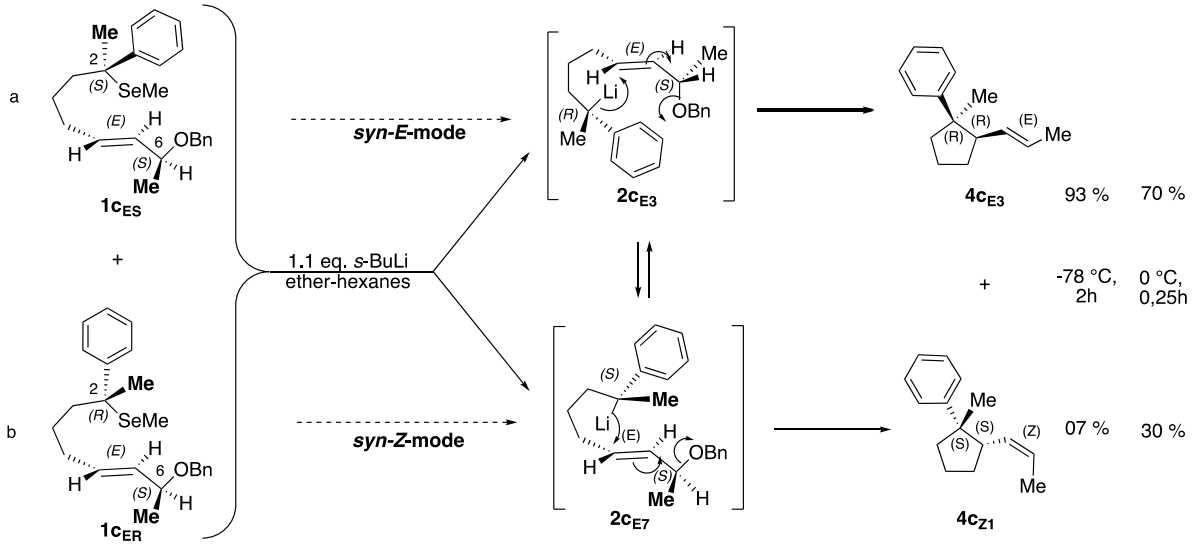
We show in Schemes 5, for each product formed, even the minor ones, the conformation of the related "transition state" and the "mode" (*syn*-mode or *anti*-mode) implied in each of their formations. It leads us, by including also the results shown in Scheme 4, to propose the following observations to rationalize the stereochemistry of the products obtained from those reactions.

(i) Reactions carried out in ether-hexane, involve the *syn*-mode, suggesting that a compact transition state is favored, in which the lithium cation is tightly linked to the benzylic carbon and coordinated by a lone pair of the alkoxy group, as well as to the π bond of the CC double bond of the allyl ether,[2,4] and those of the aromatic ring[26,27] (Schemes 4, 5, entries a,c).

(ii) Reactions carried out in THF-hexanes involve the *anti*-mode, suggesting that the intramolecular interactions discussed above no longer exist due to the selective complexation of the "lithium cation" by the lone pairs of the oxygen atoms of the more basic THF. This favors an "extended conformation" in which the complexed benzyllithium could initiate the S_N' reaction via a back-side attack, avoiding as much as possible the unfavorable steric interactions (Scheme 4,5, entries b,d).

(iii) The formation in high yields of the major stereoisomers (**4c$_{E1}$**, **4c$_{E2}$**, **4c$_{E3}$** and **4c$_{E4}$**) in reactions carried out at low temperature reported in Scheme 4, implies that each pair of epimeric unsaturated benzyllithiums **2c$_Z$** (**2c$_{ZS}$**+**2c$_{ZR}$**) and **2c$_E$** (**2c$_{ZS}$**+**2c$_{ZR}$**) generated from the corresponding benzylselenides **1c$_Z$** (**1c$_{ZS}$**+**1c$_{ZR}$**) and **1c$_E$** (**1c$_{ES}$**+**1c$_{ER}$**), epimerizes prior cyclisation to the major stereoisomers leading to **4c$_{E1}$**, **4c$_{E2}$**, **4c$_{E3}$** and **4c$_{E4}$** listed in Scheme 4 and the remainder cyclizes to the minor stereoisomers **4c$_{E3}$**, **4c$_{Z1}$**, and **4c$_{E1}$**.

The routes shown in Scheme 6 exemplify the role of the temperature on the equilibrium involved for example when the epimeric mixture of intermediates **2c$_{ES}$** and **2c$_{ER}$** are generated from **1c$_Z$** (1**c$_{ZS}$**+1**c$_{ZR}$**) and *s*-butyllithium in ether-hexane at -78 °C and 0 °C, delivering various amounts of **4c$_{E3}$** and **4c$_{Z1}$**.



Scheme 6

Structure determinations

We have not been able to separate effectively the major stereoisomers of the cyclized products **4c** in all experiments involving **1c$_Z$** and **1c$_E$** shown in Schemes 4 and 5 (entries a-d) and therefore we have not been able to determine directly their ratios and consequently their structures. We have nevertheless been able to do so by combining different techniques, taking into account: (1) that each of the four stereoisomeric (2-

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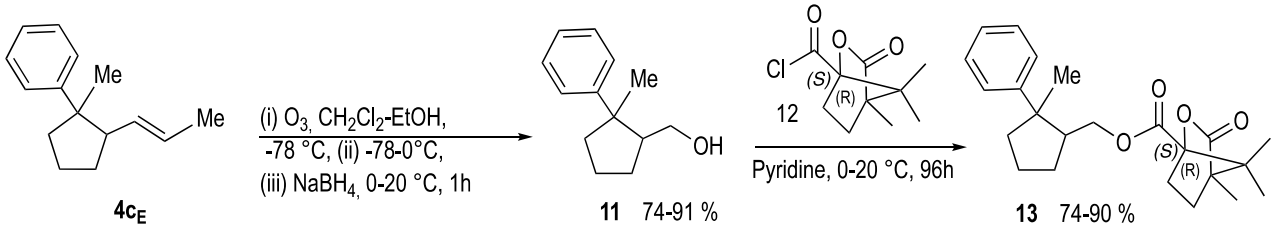
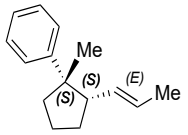
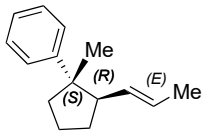
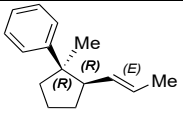
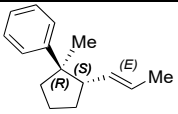
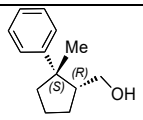
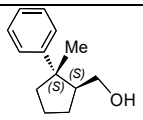
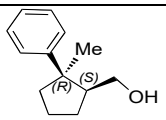
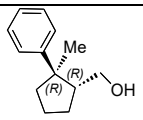
methyl-2-phenylcyclopentyl)methanols **11** (Scheme 7, Table 1, entry b) readily accessible, in a single pot process by sequential ozonolysis of the crude mixtures of **4c** followed by *in situ* reduction of the resulting ozonides with sodium borohydride,[28] has been easily separated by HPLC using a "chiral column" allowing the determination of their relative ratio in each experiment,[29] and (2) that each of the related crystalline camphenoates **13** (Scheme 7, Table 1, entries c), readily prepared by reaction of commercially available (-)-camphanic acid chloride **12** with compounds **11**,[30] has been isolated by column chromatography on SiO_2 and its structure unambiguously determined by X-ray crystallography[31] (Scheme 7, Table 1, entry d).

Finally, the stereochemistry of the CC double bond of **4c** has been assessed[32] by ^{1}H NMR spectroscopy of the crude mixtures of each experiment, taking into account the chemical shifts and value of the coupling constant of their hydrogens linked to the two adjacent vinylic carbons.



Scheme 7

Table 1.[31] Stereochemistry of compounds **4c$_E$**, **11** and **13** depicted in Scheme 7

a				
	4c$_{E1}$	**4c$_{E2}$**	**4c$_{E3}$**	**4c$_{E4}$**
b				
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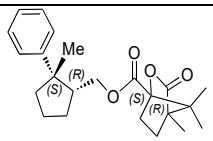
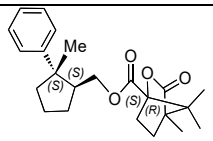
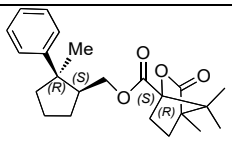
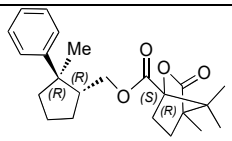
c				
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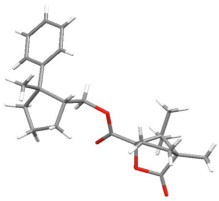
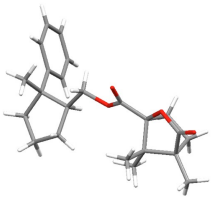
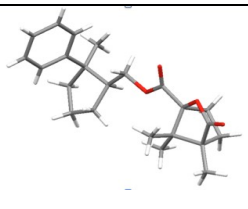
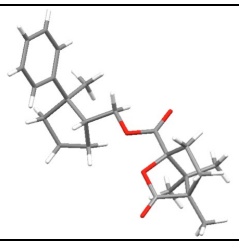
d				
	CCDC 923101	CCDC 923100	CCDC 923103[10c]	CCDC 923102

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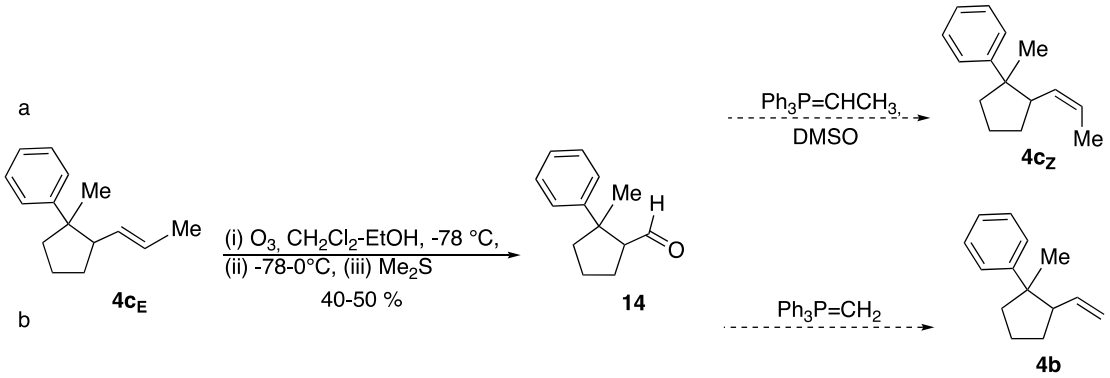
Synthetic significance of the results

We have reported above the synthesis of each of the four stereoisomers of the cyclopentane derivatives **4c$_E$** bearing a phenyl-substituted quaternary carbon next to a tertiary carbon bearing a *E*-propenyl side chain, by cyclization that produces a new bond between those two carbon atoms with unusually high stereocontrol. Those are versatile precursors of:

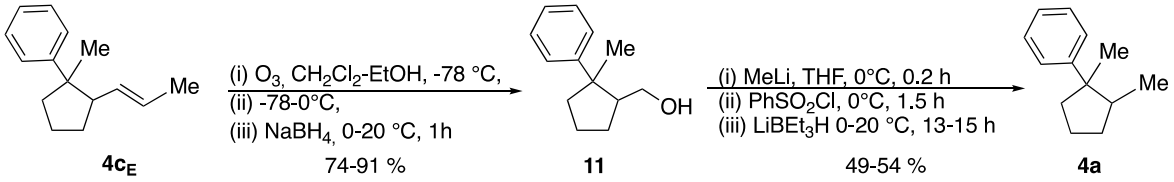
(a) The whole series of scalemic 1-phenyl-1-methyl-2-propenyl-cyclopentanes **4c$_Z$** possessing instead *Z*-propenyl moiety that cannot be obtained by carbocyclization of **1c** (Scheme 4). It would involve their sequential ozonolysis to the corresponding aldehydes **14** using ozone/dimethyl sulfide[33] followed by *Z*-stereoselective Wittig reaction using the Schlosser conditions involving ethylidenetriphenylphosphorane in DMSO[34] (Scheme 8, entry a).

(b) 1-methyl-1-phenyl-2-vinyl-cyclopentanes **4b**, previously available as racemates from 2-phenyl-2-selenomethyl-7-octene **1b** (Scheme 1, entries c,d), that can be generated by a similar method as reported in the previous paragraph (Scheme 8, entry b) but instead involving methylene triphenylphosphorane.[35]



Scheme 8

(c) Scalemic 1,2-dimethyl-1-phenyl-cyclopentanes **4a** available as racemates from 2-phenyl-2-selenomethyl-7-octene **1b** (Scheme 1, entries a,b)[1,2] that can be readily synthesized starting from the related cyclopentylmethanols **11** as outlined in Scheme 9 by reductive ozonolysis[28] of **4c$_E$** followed by sulfanylation of their hydroxyl group and reduction of the resulting sulfonates by lithium triethylborohydride (Scheme 9).[36] This set of reactions has been carried out at an early stage of our research on a racemic mixture of **4a$_{E1}$** +**4a$_{E3}$** as well as on a racemic mixture of **4a$_{E2}$** +**4a$_{E4}$** obtained from rac-**1c$_Z$** in ether-hexanes and THF-hexanes to determine their relative stereochemistry.



Scheme 9

Finally, each of the enantiomers of 1-methyl-1-methyl-2-vinyl cyclopentanes **4c$_E$** whose structures are disclosed in Scheme 4 can be produced on reaction of butyllithiums either in ether-hexanes or THF-hexanes from the different pairs of stereoisomeric benzyl selenides **1c** whose structures are shown in Scheme 10, and possessing the following characteristics:

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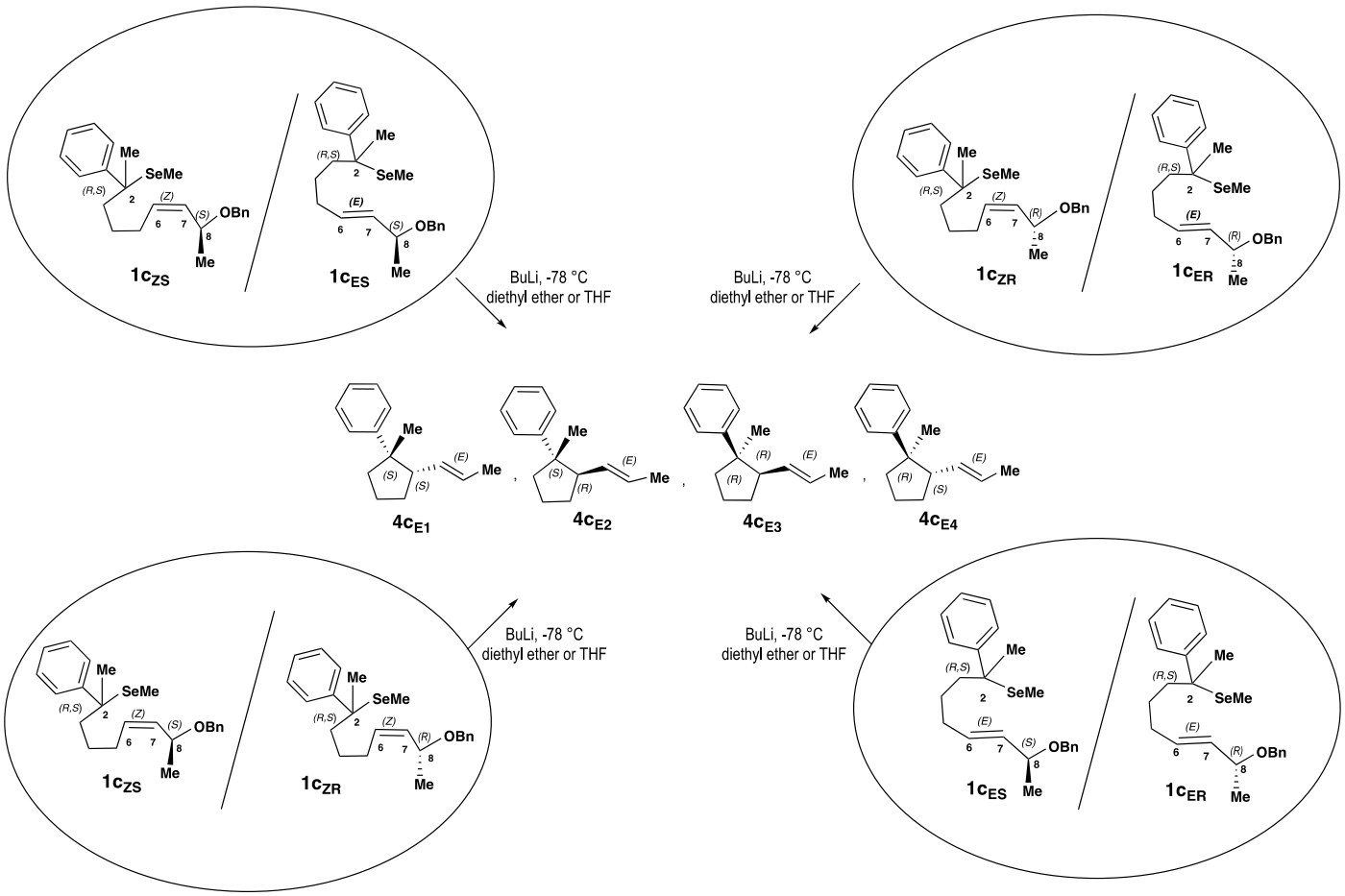
- the same (*R*)-stereochemistry at the allylic 8-positions and either a *Z*- or a *E*-CC double bond (Scheme 10, upper left),
- the same (*S*)-stereochemistry at the 8-allylic positions and a double bond possessing either a *Z* or a *E*-stereochemistry (Scheme 10, upper right),
- the same (*Z*)-stereochemistry of their CC double bonds and either an (*R*)- or (*S*)-stereochemistry at the 8-allylic position (Scheme 10, lower left)
- the same (*E*)-stereochemistry of the CC double bonds and either an (*R*)- or (*S*)-stereochemistry at the 8-allylic position (Scheme 10, lower right).



Scheme 10

Contextualization of the results

Although the allylic substitution reaction (S_N') has been the subject of extensive work[2,4,6-18] since the seminal discoveries of Winstein[37] and Stork,[14,15] it still lacks proper models to predict with confidence the outcome of any reaction belonging to that field or to suggest conditions that could allow the synthesis of any specific stereoisomer of a given substance through an S_N' reaction.[13] The intramolecular version the S_{CN}',[18] to which this work belongs, offers the advantage to avoid competing direct substitution reactions (S_N) that are usually observed. It leads to cyclic compounds, including alkenyl substituted five-membered heterocycles (Scheme 11)[11,17] and carbocycles (Scheme 12, 13) [6,18,38-40] whose stereochemistry at the carbon on the cycle bearing the alkenyl group as well as of CC double bond offer precious indications about the mechanism of the reaction.

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We first provide a brief historical background to the S_N' reaction that will allow inclusion of our work into a wider perspective.

Winstein[37] and Stork[14,15] very early recognized that the S_N' reactions could take place stereoselectively with the incoming nucleophile and the departing group lying on the same side (*syn*-mode) or the opposite side (*anti*-mode) (Figure 1).

Stork described the first *syn*-S_N' reaction[14,15] and twenty-four years later the first *anti*-S_N' reaction.[16] Since the original paper from Stork, there has been considerable discussion as to whether concerted S_N' reactions ever occur[9] and this concept has been even described in early times as "unreasonable" or "abhorrent".[9,17,41] It has then been concluded, as the result of theoretical calculations from the most influent theoretical chemists of that time, that the S_N' reaction can only proceed through the *syn*-mode (Figure 1).[5-10] Those assessments proved to be incorrect, after the experimental results reported later by Stork.[16,17]

Most of the reactions so far described did indeed involve the *syn*-mode[5-10] and generate compounds bearing usually *E*-CC double bonds,[5-10] unless it is part of a medium ring. Although products possessing the *Z*-stereochemistry have been from time to time described, often as side products,[6,12,16,17,38] they usually proceed through the *syn*-mode.

It has been reported that (i) "Experience suggests that soft nucleophiles give *syn*-stereochemistry and hard nucleophiles *anti*",[8,9,17] (ii) "Theory suggests[9] that the *syn*-mode is involved for neutral nucleophiles while anionic nucleophiles approach from the *anti*-direction"[8,9] and (iii) "Evidence is meager and contradictory…. and …. small variations produce strikingly variable results".[8,9]

Our experimental results clearly contradict those statements. We agree with the view of Overton[42] who wrote "It becomes apparent that, contrary to the long-held view that S_N' reactions proceed with *syn*-stereochemistry, the whole spectrum spanned by the *syn*- and *anti*-extremes is to be expected depending, in any particular case, on the nature of the displacing and displaced groups, counter ions, and solvent"; we propose to add "temperature". In fact, the difficulties encountered in rationalizing the results published are due to the large number of parameters that play a crucial role in the process and the widespread differences between the examples that have to be compared. Those, *inter alia*, involve: (i) the nature of the leaving group, (ii) the stereochemistry of the CC double bond, (iii) the nature, hardness of the nucleophilic atom, and nature of the counter ion for charged nucleophiles, (iv) the nature of the solvent and conformational bias resulting from the presence of the CC double bond in a cycle[5-9] either on the starting material or on the product and last but not least steric effects.[2,4-12,14-18,37-42]

We have gathered in Schemes 11-16 some typical reactions, that have appeared in the literature over the last 40 years.[5-9] They all involve as starting materials unsaturated straight-chain organometallics that produce five-membered rings[6,11,17,18,38-40] via intramolecular allylic substitution reactions leading to the departure of a benzoate (Scheme 11,[11] Scheme 12,[17] Scheme 14[18]) or an alkoxide located on the allylic site (Scheme 13,[38] Scheme 15,[39] Scheme 16[6]).

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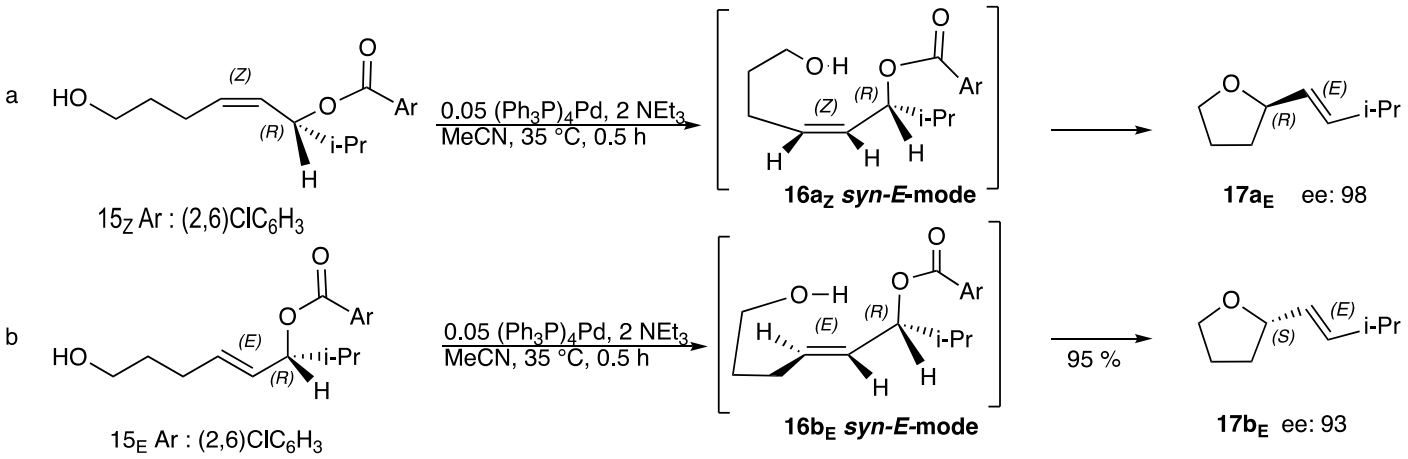
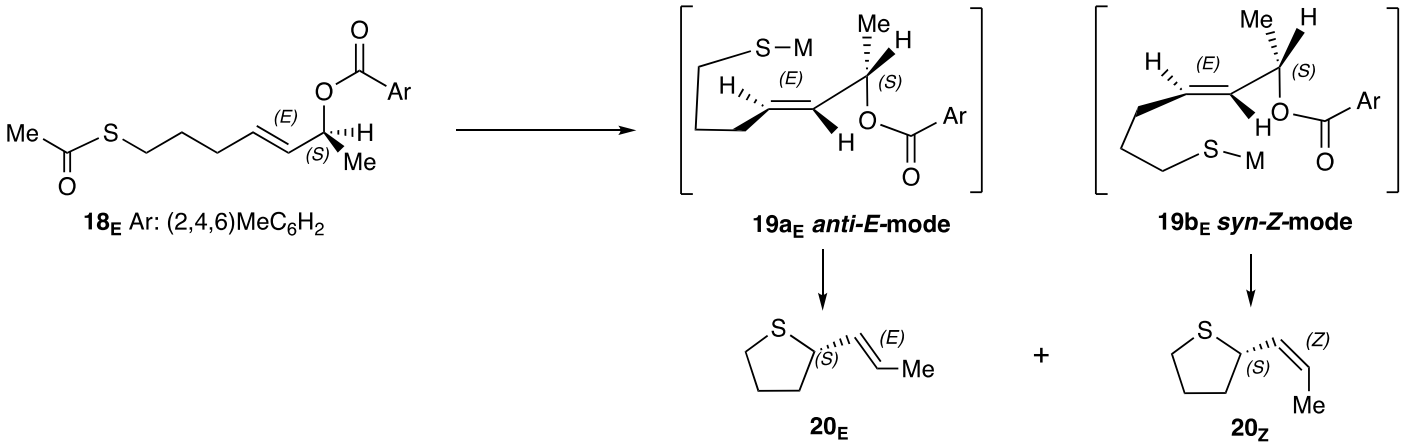
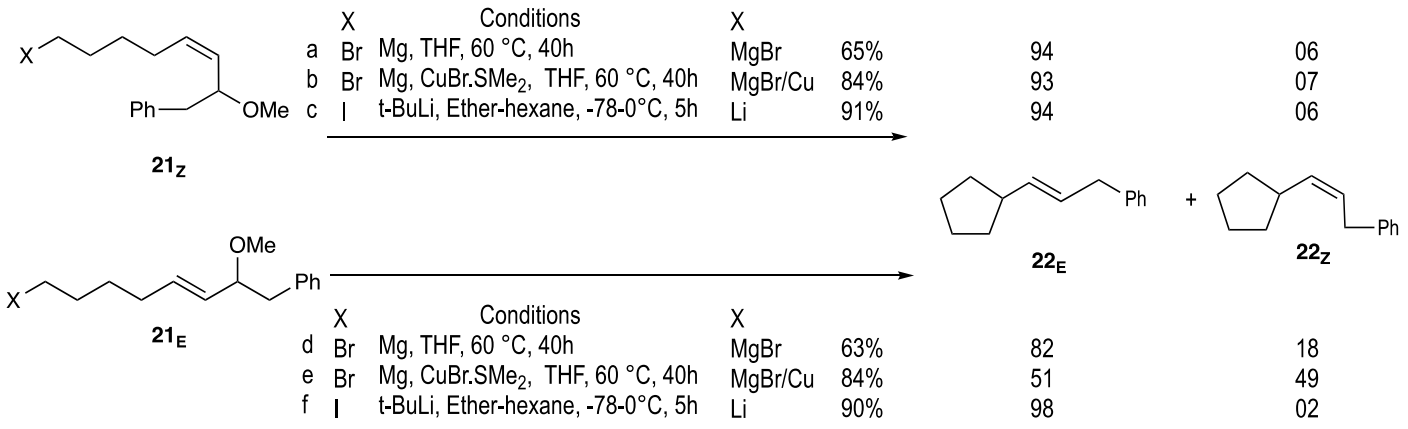


Scheme 11



a	MeOLi, THF, 20 °C, 30h	52 %	93	07
b	MeOLi, HMPA,	-	68	32
c	MeONa, THF	-	76	24

Scheme 12



	X	Conditions	X			
a	Br	Mg, THF, 60 °C, 40h	MgBr	65%	94	06
b	Br	Mg, CuBr.SMe$_2$, THF, 60 °C, 40h	MgBr/Cu	84%	93	07
c	I	t-BuLi, Ether-hexane, -78-0°C, 5h	Li	91%	94	06
d	Br	Mg, THF, 60 °C, 40h	MgBr	63%	82	18
e	Br	Mg, CuBr.SMe$_2$, THF, 60 °C, 40h	MgBr/Cu	84%	51	49
f	I	t-BuLi, Ether-hexane, -78-0°C, 5h	Li	90%	98	02

Scheme 13

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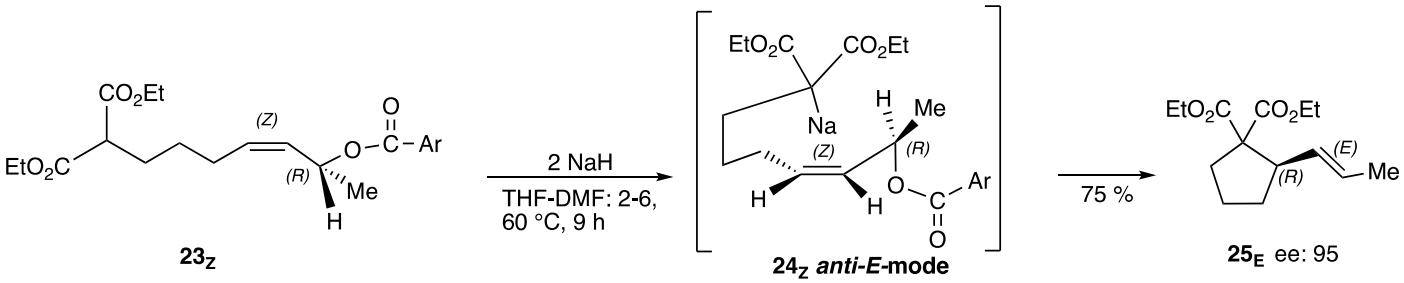
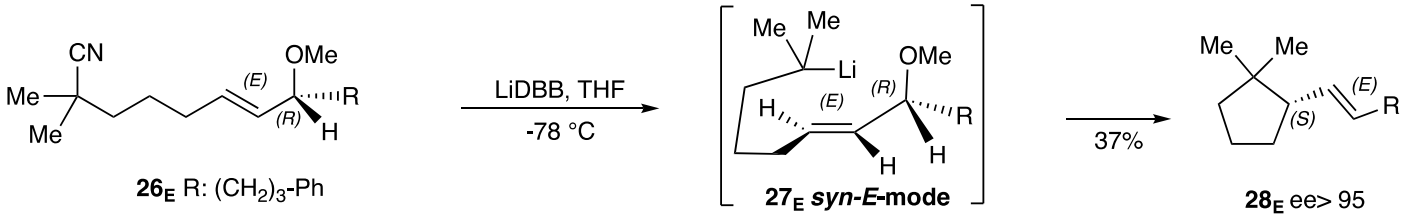


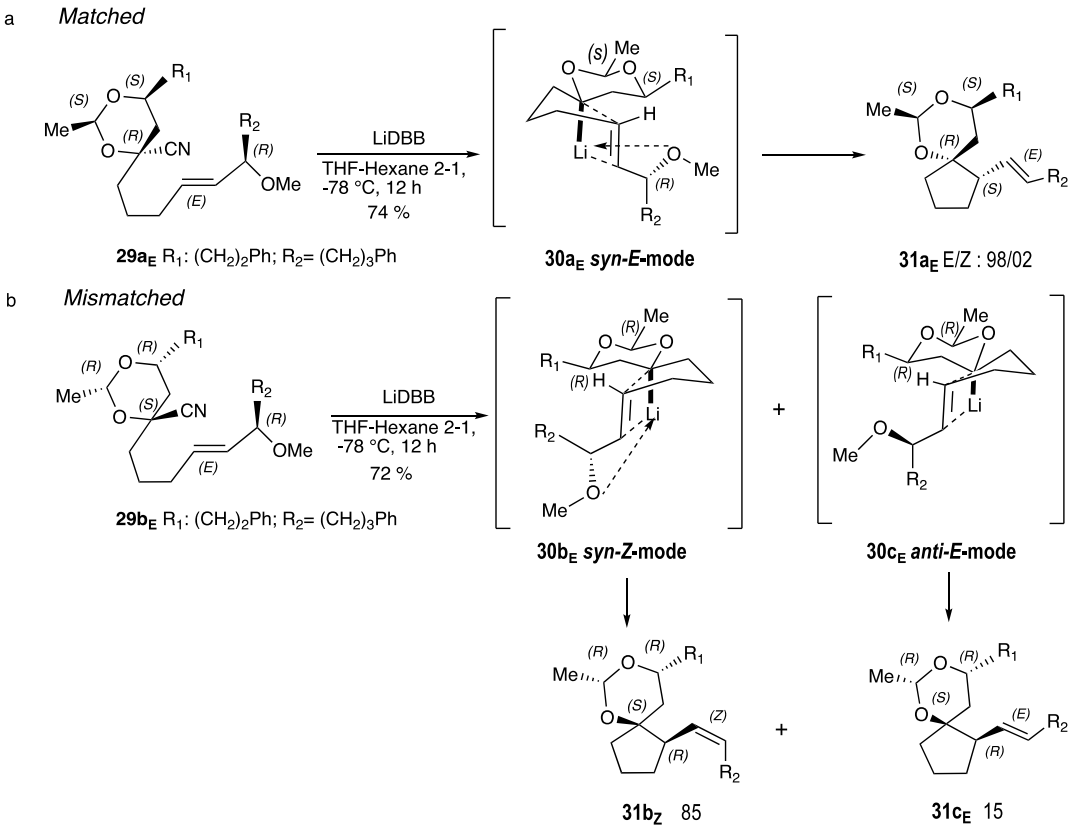
23_Z **24_Z *anti-E*-mode** **25_E** ee: 95

Scheme 14



26_E R: $(CH_2)_3$-Ph **27_E *syn-E*-mode** **28_E** ee> 95

Scheme 15



$29a_E$ R_1: $(CH_2)_2Ph$; R_2= $(CH_2)_3Ph$ **$30a_E$ *syn-E*-mode** **$31a_E$** E/Z : 98/02

$29b_E$ R_1: $(CH_2)_2Ph$; R_2= $(CH_2)_3Ph$ **$30b_E$ *syn-Z*-mode** **$30c_E$ *anti-E*-mode**

$31b_Z$ 85 **$31c_E$** 15

Scheme 16

As general trends, the reactions reported in Schemes 11-16 produce compounds in which the five-membered ring[6,11,17,18,38,39] is substituted by a *E*-CC double bond and only rarely by a *Z*-CC double bond (Scheme 12, [7] Scheme 13,[38] Scheme 16, entry b[6]).

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Most of the cyclization reactions take place through the *syn*-mode except those disclosed in Scheme 11,[17] Scheme 12[7] and Scheme 14[18] that involve instead the *anti*-mode.

One striking difference between our work and that already published is the narrow window on which we have made systematic variations (stereoisomers, solvents of same kind, temperatures) as compared to the widespread data on which correlations have been made previously (very different types of starting material, especially nucleophilic entities and leaving groups, have been studied, using a wide variety of solvents and temperatures).

As general trends, S_N' reactions that involve a metal cation[5-8] or eventually a proton,[43] favor, as in our case, highly structured transition states involving chelation by atoms bearing lone pairs and π-bonds leading to the *syn*-mode. However this organization can be prevented when the reactions are performed in polar solvents, at high temperature or in cases of unfavorable steric interactions[5-8] favoring thus the *anti*-mode.

We did not find experimental proofs confirming the assessment of Stille[38] that the reactions disclosed in Scheme 13 proceed through an *anti*-mode, and we rationalize the *anti*-mode involved in the reactions implying metal thiolates[17] (**19a**, Scheme 12) or a metal malonate[18] (**24**, Scheme 14) by poorer chelation of (i) the soft thiolate[17] to the hard counter-cation (**19**, Scheme 12) and (ii) the delocalized enolate in case of the sodio-malonate[18] (**24**, Scheme 14) that disfavor the chelated preorganization leading to the *syn*-mode.

The case of α-alkoxyalkenyl lithiums **30a$_E$** and **30b$_E$** (Scheme 16)[6] attracted our attention since it shares some similarity with that of α-phenyl alkenyllithiums **2$_E$** we have disclosed in Schemes 4 and 5 (entry c). They all bear a CC double bonds possessing the *E*-stereochemistry and a quaternary carbanionic center to which are attached groups (alkoxy and phenyl respectively) able to coordinate the lithium cation. They both deliver, through a *syn*-mode, cyclopentane derivatives in which those groups are *cis* to the pending CC double bonds (**31a$_E$**, **31b$_Z$**, **4c$_{E3}$**, **4c$_{Z1}$**), and last but not least whereas one of the organolithium epimers delivers cyclopentane derivatives possessing *E*-CC double bonds through the *syn*-*E*-mode (**31a$_E$**, Scheme 16, entry a; **4c$_{E3}$**, Scheme 6, entry a) the other unusually produce mainly its stereoisomers possessing *Z*-CC double bonds (**31b$_Z$**, Scheme 16, entry b; **4c$_{Z1}$**, Scheme 6, entry b) through the *syn*-*Z*-mode.

There are however striking differences, since (i) α-alkoxyalkenyl lithiums **30a$_E$** and **30b$_E$** are expected to be configurationally stable,[6,44] whereas benzyl lithiums such **2c$_{E7}$** and **2c$_{E3}$** have been found to interconvert already at -78 °C.[19,20] This did not prove to be a problem because the latter have been found to adapt to the experimental conditions; (ii) although correlations about the outcome of the two types of reaction disclosed above fit very well (compare Schemes 4,5; entries c with Scheme 16, *syn*-mode in each case), they have been carried out in different solvents (THF for α-alkoxyalkenyl lithiums **30$_E$** and ether for α-phenylalkenyl lithiums **2$_E$**) that have been found, at least for α-phenylalkenyl lithiums (compare Schemes 4,5; entries c with entries d), to lead to very different stereochemical outcome: *syn*-mode in ether, *anti*-mode in THF! We assume therefore that THF does not affect the ability of the alkoxy-group attached to the carbanionic center of **30$_E$** to complex the "lithium cation" that leads to the compact transition state required for the *syn*-mode, whereas it destroys the weaker complexation of the same cation by the electron cloud of the phenyl ring[1,2,4,26,27] in α-phenyl-alkenyl lithiums **2$_E$** that is only observed when the less basic ether is instead used.

Synthesis of the starting materials

The multistep syntheses of two isomeric *Z*- and *E*-[(8*S*)-8-(benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selane **1c$_Z$** and **1c$_E$**, reported in Scheme 17 and Scheme 18 respectively, follows the retrosynthetic analysis shown in Scheme 3. Each of them was carried out from the commercially available (*S*)-3-but-3-yn-2-ol **5**[21] and involve in each case protection of its hydroxyl group that allow the stepwise alkylation of their terminal acetylenic

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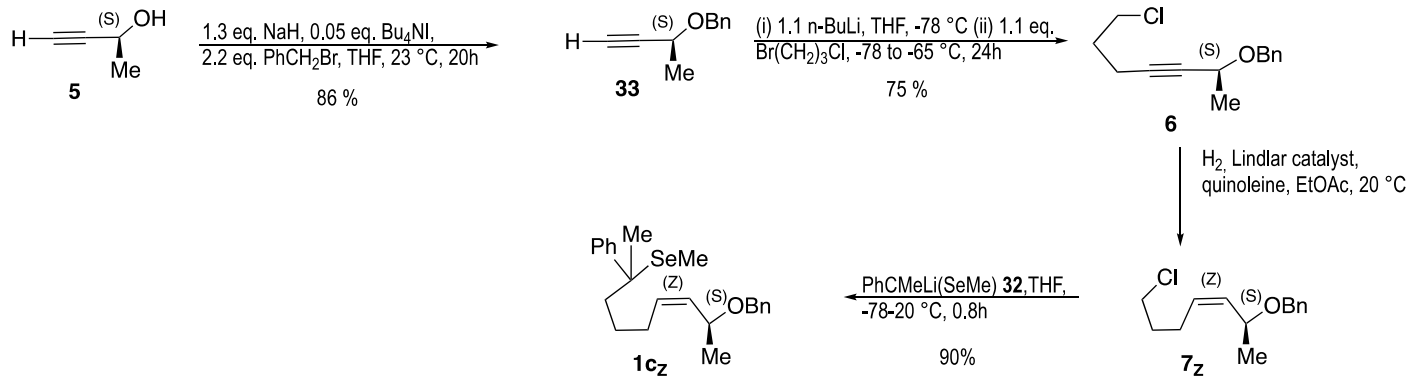
carbon and at the last stage the introduction of a benzylseleno moiety through the corresponding α-selenobenzyl lithium **32**.[1,2,25]

The synthesis of the *Z*-stereoisomer **1c$_Z$** involves the shortest of the two routes (Scheme 17) that uses the benzyl protected propargylic alcohol **33** its metalation by *n*-butyllithium in THF-hexanes at -78 °C and subsequent alkylation of the resulting acetylide by 1-bromo-3-chloropropane that takes place selectively on the carbon bearing the bromine atom, finally leading to **6** in 75 % yield. Catalytic dihydrogenation of **6** generates **7$_Z$** in 85 % yield possessing a *Z*-CC double bond was achieved using Lindlar catalyst[22] in the presence of quinoleine to avoid over reduction and the formation of the target compound **1c$_Z$** has been achieved in 90 % yield by reacting the chloride **7$_Z$** with 1-phenyl-1-methylseleno-ethyllithium **32**.[1,2,25]



Scheme 17

The synthesis of the *E*-stereoisomer **1c$_E$** (Scheme 18) is lengthier due to the exchange of the original *tert*-butyl dimethylsilyl protecting group that is required to allow the metalation/alkylation process leading to **35** but needs to be removed to offer one hand to carry the stepwise introduction of the two hydrogens in a *trans*-relationship on the CC double bond using RedAl[23] followed by the hydrolysis of the resulting aluminum alcoholate leading to **9$_E$**.

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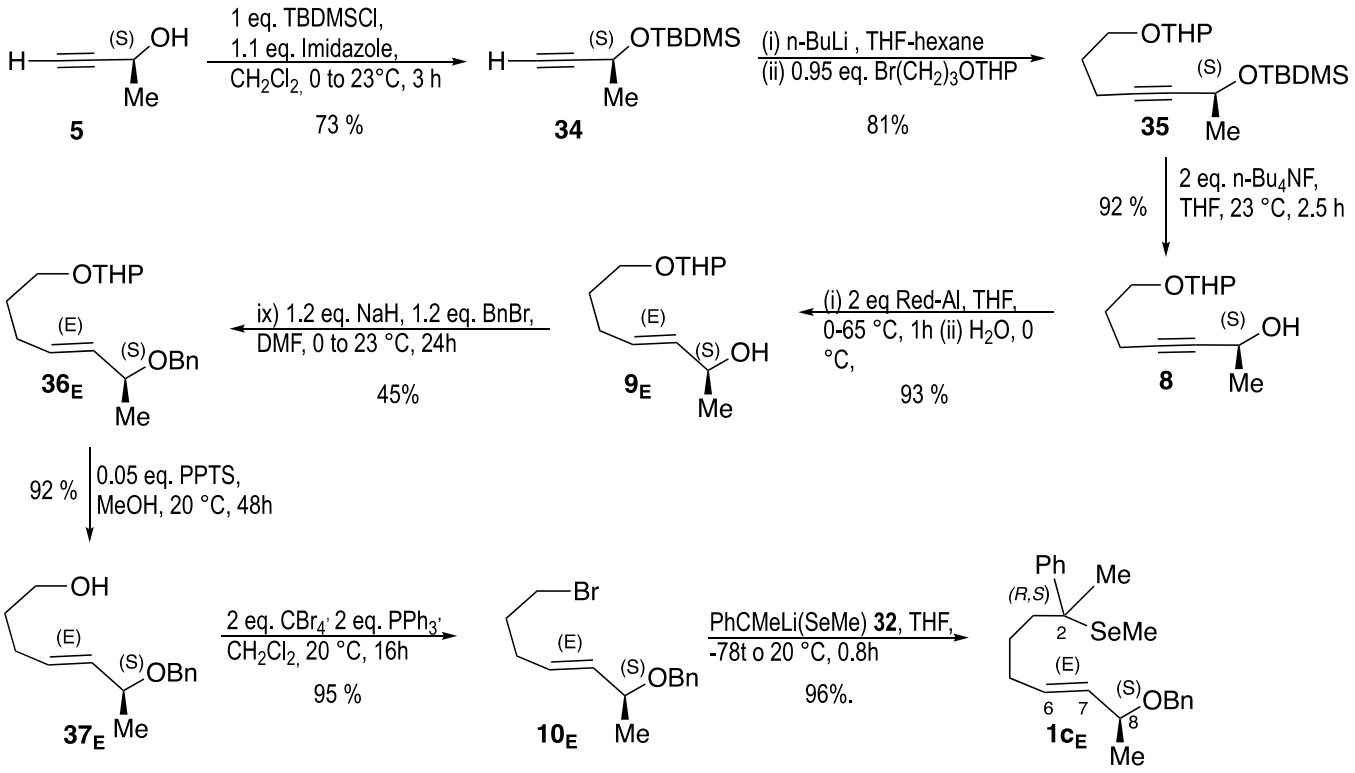

Scheme 18

An orthogonal deprotection/protection was required to avoid inadequate deprotection of the THP group and to promote the requested benzylation of the allyl alcohol moiety leading to **36**$_E$. Selective deprotection of the THP group leaving untouched the benzyloxy ether was achieved by acid catalyzed methanolysis leading to the alcohol **37**$_E$ that on reaction with carbon tetrabromide/triphenylphosphine reagent[46] leads to the *E*-unsaturated bromide **10**$_E$ pendant of *Z*-unsaturated chloride **7**$_E$ whose reaction with 1-phenyl-1-(methylseleno)ethyl lithium **32**[1,2,25] provides stereoselectively **1c**$_E$.

Conclusions

The results reported not only allow the stereodirected synthesis of a large variety of phenylcyclopentane derivatives but also provide coherent experimental data about the stereochemical outcome of a specific S_N' reaction that gathers crucial information about the effect of different structural features on the stereochemistry of the products. We expect that further work can provide crucial contextual information by changing sequentially the metal (Na, Mg, K, or Cu,..), the leaving group at the allylic carbon (metal alkoxides, alkoxy group, sulfonates or halides,..), the substitution at the benzylic carbon (H, alkyl-, alkoxy-, thioalkyl-, or selenoalkyl-groups) or on the CC double bond (alkyl groups at C-6, C-7; OC*H-OR or 2H at C-8)] and experimental variations (solvents, additive, temperature). This process could also be extended to the stereoselective synthesis of a large variety of arylcycloalkanes involving the concomitant formation of three,[45] six and even higher membered rings as well as scalemic allenes from starting material bearing a propargyl ether[45] instead of an allyl ether moiety.[4] They could then serve as a model to predict with confidence the stereochemical outcome of any S_N' reactions.

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Experimental Section

General. (i) Thin layer chromatography (TLC) was conducted on pre-coated aluminum sheets with 0.20 mm Machevery-Nagel Alugram SIL G/UV254 with fluorescent indicator UV254. Column chromatography was carried out using Merck Gerduran silica gel 60 (particle size 63-200 μm) (ii) Melting points (M.p.) were measured on a Büchi Melting Point B-545 in open capillary tubes and have not been corrected. (iii) Nuclear magnetic resonance (NMR) ^{1}H, ^{13}C and ^{19}F spectra were obtained on a 400 MHz NMR (Jeol JNM EX-400) Chemical shifts were reported in ppm according to tetramethylsilane using the solvent residual signal as an internal reference ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm). Coupling constants (J) were given in Hz (J_1: ortho, J_2: meta, J_3: para). Resonance multiplicity was described as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), q (quartet), m (multiplet) and br (broad signal). Carbon spectra were acquired with a complete decoupling for the proton. (iv) Infrared spectra (IR) were recorded on a Perkin-Elmer Spectrum II FT-IR System single-reflection ATR mounted with a diamond mono-crystal (v) Chiral high-performance liquid chromatography (HPLC) analysis were performed through a chiral analytical column CHIRALCEL OJ-H (Daicel Chemical Industries, Ltd.) (0.25 m × 4.6 mm) coated with tris-(4-methylbenzoate) cellulose on 5 μm silica-gel substrate). Column type: Eluent: n-Hexane/i-Propanol 99/1; Flow rate: 2 ml/min, Injection: 10 μl of a 5 mg/ml solution, Detection: UV (220 nm), Peaks at: 14.4 min (**11_1**), 21.2 min (**11_2**), 24.5 min (**11_3**), 33.3 min (**11_4**) using a Merck-Hitachi 655A equipment using a UV detector (vi) X-ray analyses have been carried out by the "Laboratoire de Chimie Moléculaire Structurale", UNamur using NOMIUS CAD-4 diffractometer and the K_α ray of copper (λ: 1.54178 nm). Product's structures have been resolved with the program SIR92 and refined with the program SHELXL97. CCDC quotation refers to the crystal structures related to **13_1**-**13_4** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers: **13_1** (CCDC 923101), **13_2** (CCDC 923100), **13_3** (CCDC 923103), **13_4** (CCDC 923102) (vii) Chemicals were purchased from Sigma Aldrich, Acros Organics, TCI and ABCR and were used as received. Solvents were purchased from Sigma Aldrich, while deuterated solvents from Eurisotop. Diethyl ether and THF were distilled from sodium-benzophenone-cetyl, toluene was refluxed over calcium hydride and dichloromethane (CH_2Cl_2) was refluxed over phosphorus pentoxide. Anhydrous DMF was purchased from Acros Organics. Hydrochloric acid (HCl 32%) was purchased from Fischer Scientific. MeOH and $CHCl_3$ were purchased as reagent-grade and used without further purification (viii) Low temperature baths were prepared using different solvent mixtures depending on the desired temperature: -78°C with acetone/dry ice, -40 °C with CH_3CN/liquid N_2, -10 °C with ice-H_2O/NaCl, and 0 °C with ice/H_2O. Anhydrous conditions were achieved by drying 2-neck flasks by flaming with a heat gun under vacuum and then purging with argon. The inert atmosphere was maintained using argon-filled balloons equipped with a syringe and needle that was used to penetrate the silicon stoppers used to close the flasks' necks. Additions of liquid reagents were performed using dried plastic or glass syringes.

A. Cyclization of [(8*S*)-8-(benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selanes (**$1c_E$ and $1c_Z$**)

Reaction of $1b_Z$ with *n*-BuLi in THF at -78 °C (General procedure 1). To a flask containing [(8*S*,*Z*)-8-(benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selane (**$1c_Z$**, 200 mg, 0.5 mmol) in dry THF (5 mL) was added dropwise at -78 °C a solution of *n*-BuLi (1.6 M in hexanes, 0.31 mL, 0.5 mmol) and the reaction mixture was stirred for 2 h at -78 °C. MeOH (1 mL) was added at the same temperature, the reaction mixture was warm to 23 °C, diluted with Et_2O (60 mL) and washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane) to give a mixture of **$4b_{E2}$** and **$4b_{E3}$** (65 mg, 65% yield) in a 94/6 ratio.

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Reaction of $1b_E$ with *s*-BuLi in Et_2O at -78 °C (General procedure 2). To a flask containing [(8*S*,*E*)-8-(benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selane (**$1c_E$**, 200 mg, 0.5 mmol) in dry Et_2O (5 mL) was added dropwise at -78 °C a solution of *s*-BuLi (1.4 M in cyclohexane, 0.36 mL, 0.5 mmol) and the reaction mixture was stirred for 2 h at -78 °C. MeOH (1 mL) was added at the same temperature, the reaction mixture was warm to 23 °C, diluted with Et_2O (60 mL) and washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane) to give a mixture of **$4c_{E3}$** and **$4c_{Z1}$** (88 mg, 88% yield) in a 93/7 ratio.

$4c_{E1}$ *and* **$4c_{E3}$:** ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.30-7.23 (m, 2H), 7.23-7.18 (m, 2H), 7.18-7.12 (m, 1H), 5.35 (dqd, *J* 15.2, 6.4, 0.8, 1H), 4.87 (ddq, *J* 15.1, 8.7, 1.6, 1H), 2.46-2.36 (m, 1H), 2.28-2.17 (m, 1H), 1.94-1.70 (m, 4H), 1.56-1.43 (m, 1H), 1.53 (dd, *J* 6.4, 1.6, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 147.0, 133.2, 127.6, 127.4, 125.2, 124.7, 54.3, 49.8, 38.1, 30.8, 29.0, 22.1, 17.9. Chiral HPLC [column: DAICEL CHIRALPAK OJ + OJ-H; solvent: hexane/i-propanol = 99.5/0.5; flow rate: 0.2 ml/min; detection: 220 nm]: 39.5 min and 40.5 min. Due to overlapping of the two peaks, the enantiomeric excess was measured on the corresponding alcohols **11_1** and **11_3**. Anal. calc. for $C_{15}H_{20}$: C, 89.94, H, 10.06; found C, 89.78, H, 9.96%.

$4c_{E2}$ *and* **$4c_{E4}$:** ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.44-7.37 (m, 2H), 7.33-7.24 (m, 2H), 7.21-7.13 (m, 1H), 5.49-5.29 (m, 2H), 2.74-2.65 (m, 1H), 2.10-1.61 (m, 6H), 1.65 (d, *J* 5.9, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 149.9, 131.9, 127.9, 126.1, 125.5, 125.3, 52.8, 48.6, 41.7, 30.6, 21.9, 21.8, 18.2,; Chiral HPLC [column: DAICEL CHIRALPAK OJ + OJ-H; solvent: hexane/i-propanol = 99.5/0.5; flow rate: 0.2 ml/min; detection: 220 nm]: 48.2 min and 50.7 min. Due to overlapping of the two peaks, the enantiomeric excess was measured on the corresponding alcohols **11_2** and **11_4**. Anal: calc. for $C_{15}H_{20}$ C, 89.94, H, 10.06; found: C, 89.85, H, 10.08%.

$4c_{Z1}$: ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.25-7.20 (m, 2H), 7.19-7.13 (m, 1H), 5.30 (dqd, *J* 10.9, 6.9, 0.8, 1H), 4.85 (ddq, *J* 10.9, 10.3, 1.6, 1H), 2.92 (dt, *J* 10.3, 7.1, 1H), 2.30-2.20 (m, 1H), 2.05-1.72 (m, 5H), 1.67 (dd, *J* 6.9, 1.6, 3H), 1.34 (s, 3H).

B. Synthesis of (2-methyl-2-phenylcyclopentyl)methanol (**11**)

Synthesis of [(1*S*,2*S*)-2-methyl-2-phenylcyclopentyl]methanol (**11_1**) **(General procedure 3)**. To a flask containing {(1S,2R)-1-methyl-2-[(*E*)-prop-1-en-1-yl]cyclopentyl}benzene (**$4c_{E1}$**, 40 mg, 0.2 mmol) in a mixture of dry CH_2Cl_2 (8 mL) and dry MeOH (8 mL) was bubbled O_3 in the solution at -78 °C for 2 min. The solution was purged with argon for 15 minutes and allowed to warm to 0 °C. $NaBH_4$ (40 mg, 1 mmol) was added and the solution stirred at 0 °C for 1 h.[28] The solvents were removed under reduced pressure and the residue diluted with Et_2O (50 mL), washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 75:25) to give **11_1** (28 mg, 74% yield).

11_1 and **11_3:** Mp: 44 °C; ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.35-7.28 (m, 4H), 7.24-7.16 (m, 1H), 3.33 (dd, *J* 10.9, 5.4, 1H), 3.03 (dd, *J* 10.9, 8.1, 1H), 2.25-2.07 (m, 2H), 2.06-1.95 (m, 1H), 1.95-1.72 (m, 3H), 1.70-1.58 (m, 1H), 1.38 (s, 3H), 1.35 (s, 1H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 146.9, 128.1, 126.9, 125.7, 64.6, 52.3, 48.5, 37.3, 29.9, 27.4, 21.8; IR (solid): 3343, 2956, 2878, 1495, 1444, 1065, 1016, 766, 703, 611, 560 cm^{-1}. Chiral HPLC [column: DAICEL CHIRALPAK OJ-H; solvent: hexane/i-propanol = 99/1; flow rate: 2 ml/min; detection: 220 nm]: 14.4 min (**11_1**) and 24.5 min (**11_3**). Anal: calc. for $C_{15}H_{20}$: C, 82.06, H, 9.54; found C, 81.80, H, 9.58%.

11_2 *and* **11_4:** ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.46-7.40 (m, 2H), 7.36-7.29 (m, 2H), 7.23-7.16 (m, 1H), 3.71 (dd, *J* 10.6, 5.7, 1H), 3.53 (dd, *J* 10.6, 8.1, 1H), 2.48-2.37 (m, 1H), 2.14-1.99 (m, 2H), 1.91-1.71 (m, 3H), 1.62-1.50 (m, 1H), 1.44 (s, 1H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 149.3, 128.2, 125.8, 125.6, 64.4, 52.9, 47.3, 43.6, 28.4, 22.3, 20.3; IR (film): 3339, 2957, 2873, 1496, 1444, 1075, 1029, 997, 758, 698, 550 cm^{-1}. Chiral HPLC [column: DAICEL CHIRALPAK OJ-H; solvent: hexane/i-propanol = 99/1; flow rate: 2 ml/min;

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detection: 220 nm]: 21.2 min (11_2) and 33.3 min (11_4). Anal: calc. for $C_{15}H_{20}$: C, 82.06, H, 9.54; found C, 80.93, H, 9.54%.

C. Synthesis of (2-methyl-2-phenylcyclopentyl)methyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]-heptane-1-carboxylate (**13**)

[(1*R*,2*S*)-2-Methyl-2-phenylcyclopentyl]methyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**13_1**) **(General procedure 4)**. To a flask containing [(1*S*,2*S*)-2-methyl-2-phenyl-cyclopentyl]methanol (**11_1**, 28 mg, 0.15 mmol) in dry pyridine (0.5 mL) was added at 0 °C (1*S*)-(-)-camphanic chloride[30] (36 mg, 0.165 mmol) and the reaction mixture was stirred for 4 days at 23 °C. The reaction mixture was diluted with Et_2O (50 mL) and washed with 6 M aq. HCl (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 80:20) to give **13_1** (50 mg, 90% yield).

13_1: Mp: 84 °C; ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.35-7.23 (m, 4H), 7.21-7.15 (m, 1H), 3.90 (dd, *J* 10.8, 4.8, 1H), 3.62 (dd, *J* 10.9, 9.5, 1H), 2.41-2.29 (m, 2H), 2.28-2.16 (m, 1H), 2.07-1.76 (m, 6H), 1.72-1.52 (m, 2H), 1.38 (s, 3H), 1.10 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 178.3, 167.5, 146.2, 128.2, 126.9, 125.9, 91.1, 67.7, 54.8, 54.1, 48.8, 48.4, 37.2, 30.6, 29.9, 28.9, 27.6, 21.7, 16.8, 16.7, 9.7; IR (film): 2963, 1785, 1744, 1446, 1309, 1262, 1170, 1104, 1059, 1018, 993, 931, 772, 706, 564 cm^{-1}.

13_2: Mp: 105 °C; ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.43-7.37 (m, 2H), 7.34-7.27 (m, 2H), 7.21-7.14 (m, 1H), 4.24 (dd, *J* 10.9, 6.1, 1H), 4.15 (dd, *J* 11.0, 8.5, 1H), 2.67-2.56 (m, 1H), 2.20-2.10 (m, 1H), 2.10-1.98 (m, 2H), 1.89-1.72 (m, 5H), 1.67-1.54 (m, 2H), 1.26 (s, 3H), 1.07 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 178.1, 167.5, 148.6, 128.2, 125.9, 125.7, 91.1, 67.1, 54.7, 54.0, 48.1, 47.5, 43.8, 30.4, 28.9, 28.6, 22.2, 20.6, 16.7, 9.7; IR (film): 2958, 1781, 1744, 1445, 1307, 1260, 1172, 1108, 1061, 1020, 996, 934, 797, 754, 699, 513 cm^{-1}.

13_3: Mp: 91 °C; ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.34-7.27 (m, 4H), 7.22-7.15 (m, 1H), 3.92 (dd, *J* 11.0, 4.8, 1H), 3.62 (dd, *J* 10.9, 9.5, 1H), 2.41-2.29 (m, 2H), 2.28-2.18 (m, 1H), 2.05-1.77 (m, 6H), 1.72-1.57 (m, 2H), 1.39 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 178.2, 167.5, 146.2, 128.2, 126.9, 126.0, 91.1, 67.6, 54.8, 54.1, 48.9, 48.5, 37.2, 30.6, 29.9, 28.9, 27.5, 21.7, 16.8, 16.7, 9.7; IR (film): 2964, 1775, 1747, 1466, 1310, 1274, 1172, 1109, 1061, 1019, 992, 964, 932, 764, 701, 591, 511 cm^{-1}.

13_4: Mp: 117 °C; ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.43-7.37 (m, 2H), 7.35-7.28 (m, 2H), 7.20-7.15 (m, 1H), 4.27-4.15 (m, 2H), 2.68-2.57 (m, 1H), 2.24-2.14 (m, 1H), 2.12-1.97 (m, 2H), 1.91-1.73 (m, 5H), 1.68-1.55 (m, 2H), 1.27 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H), 0.91 (s, 3H)); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 178.1, 167.5, 148.5, 128.3, 125.8, 91.1, 67.1, 54.7, 54.0, 48.0, 47.5, 43.7, 30.3, 28.9, 28.6, 22.1, 20.7, 16.7, 9.7; IR (film): 2965, 1780, 1721, 1446, 1316, 1275, 1167, 1105.

D. Synthesis of [(8*S*,*Z*)-8-(benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selane 1b$_Z$

(*S*)-[(But-3-yn-2-yloxy)methyl]benzene (**33**). To a flask containing a suspension of NaH (60% dispersion in oil, 364 mg, 9.1 mmol) and a catalytic amount of Bu_4NI (130 mg, 0.35 mmol) in dry THF (14 mL) was added dropwise a solution of (*S*)-but-3-yn-2-ol (**5**, 490 mg, 7 mmol) in dry THF (2 mL) and the mixture was stirred for 45 min. BnBr (2.63 g, 1.8 mL, 15.4 mmol) was added dropwise and the reaction mixture stirred for 20 h (formation of a white precipitate after 1 h). The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with pentane (3 × 25 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 99:1 to 95:5) to give **33** (960 mg, 86% yield). Spectral data for **33** match those previously reported.[47]

(*S*)-{[(7-Chlorohept-3-yn-2-yl)oxy]methyl}benzene (**6**). To a flask containing (S)-[(but-3-yn-2-yloxy)methyl]-benzene **33** (960 mg, 6 mmol) in dry THF (10 mL) was added dropwise at –78 °C a solution of *n*-BuLi (1.6 M in

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hexanes, 4.12 mL, 6.6 mmol) and the mixture was stirred for 15 min. A solution of 1-bromo-3-chloropropane (1.04 g, 6.6 mmol) in dry THF (3 mL) was added dropwise and the reaction mixture was heated at 65 °C and stirred for 24 h. After cooling, the reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 35 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 96:4) to give **6** (1.06 g, 75% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.40-7.26 (m, 5H), 4.76 (d, *J* 11.7, 1H), 4.49 (d, *J* 11.7, 1H), 4.20 (qt, *J* 6.6, 1.8, 1H), 3.67 (t, *J* 6.4, 2H), 2.45 (td, *J* 6.8, 1.8, 2H), 1.98 (quint, *J* 6.4, 2H), 1.44 (d, *J* 6.6, 3H).

(*S,Z*)-{[(7-Chlorohept-3-en-2-yl)oxy]methyl}benzene (**7$_Z$**). To a flask containing (*S*)-{[(7-chlorohept-3-yn-2-yl)oxy]methyl}benzene (**6**, 710 mg, 3 mmol) in EtOAc (10 mL) were added quinoline (60 µL) and Lindlar's catalyst (300 mg) and the reaction mixture was stirred at 23 °C under an atmosphere of H_2. After 4 h, the reaction mixture was filtered over Celite (Et_2O eluent) and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 96:4) to give **7$_Z$** (610 mg, 85% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.39-7.24 (m, 5H), 5.55-5.41 (m, 2H), 4.55 (d, *J* 11.8, 1H), 4.37 (d, *J* 11.8, 1H), 4.37-4.29 (m, 1H), 3.52 (t, *J* 6.5, 2H), 2.25-2.16 (m, 2H), 1.83 (quint, *J* 6.8, 2H), 1.27 (d, *J* 6.4, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 138.8, 133.7, 130.1, 128.3, 127.7, 127.4, 70.1, 69.9, 44.3, 32.3, 24.7, 21.6.

[(8*S,Z*)-8-(Benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selane 1c$_Z$. To a flask containing (1-phenylethane-1,1-diyl)bis(methylselane) (771 mg, 2.64 mmol) in dry THF (10 mL) was added dropwise at -78 °C a solution of *n*-BuLi (1.6 M in hexanes, 1.51 mL, 2.42 mmol) and the reaction mixture was stirred for 40 min (yellow solution of **32**). A solution of (*S,Z*)-{[(7-chlorohept-3-en-2-yl)oxy]methyl}benzene **7$_Z$** (525 mg, 2.2 mmol) in dry THF (5 mL) was added dropwise and the reaction mixture stirred at -78 °C for 1.5 h and at 23 °C for 1.5 h (discoloration). MeOH (1 mL) was added, the reaction mixture diluted with Et_2O (75 mL), washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 96:4) to give **1c$_Z$** (788 mg, 90% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.48-7.42 (m, 2H), 7.38-7.22 (m, 7H), 7.21-7.14 (m, 1H), 5.53-5.43 (m, 1H), 5.41-5.31 (m, 1H), 4.58-4.48 (m, 1H), 4.37-4.19 (m, 2H), 2.25-2.14 (m, 1H), 2.08-1.91 (m, 3H), 1.83 (s, 3H), 1.70 (s, 3H), 1.48-1.33 (m, 1H), 1.33-1.09 (m, 4H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 145.1, 138.8, 132.5, 131.8, 128.3(1), 128.2(9), 128.1, 127.4, 126.8, 126.2, 70.0(5), 69.9(7), 69.8, 69.7, 46.5, 42.4(4), 42.4(1), 27.7, 26.2, 25.2, 21.5(7), 21.5(5), 3.3; IR (film): 2926, 1495, 1453, 1445, 1368, 1131, 1089, 1065, 1028, 900, 733, 695, 656 cm^{-1}.

E. Synthesis of [(8*S,E*)-8-(benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selane (**1c$_E$**)

(*S*)-(But-3-yn-2-yloxy)(*tert*-butyl)dimethylsilane (**34**). To a flask containing (*S*)-but-3-yn-2-ol (**5**, 1.40 g, 20 mmol) in dry CH_2Cl_2 (16 mL) was added at 0 °C imidazole (1.50 g, 22 mmol) and the mixture was stirred for 10 min. TBDMSCl (3.01 g, 20 mmol) was added and the reaction mixture was stirred at 0 °C for 15 min and then at 23 °C for 3 h (formation of a white precipitate after 1 h). The reaction mixture was diluted with H_2O (10 mL) and extracted with pentane (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane) to give **34** (2.70 g, 73% yield). Spectral data for **34** match those previously reported.[48]

***tert*-Butyldimethyl({(2*S*)-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]hept-3-yn-2-yl}oxy)silane** (**35**). To a flask containing (*S*)-(but-3-yn-2-yloxy)(*tert*-butyl)dimethylsilane **34** (2.21 g, 12 mmol) in dry THF (40 mL) was added dropwise at -30 °C a solution of *n*-BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol) and the mixture was stirred for 30 min. The reaction mixture was cooled to -78 °C, dry HMPA (5 mL) was added and the solution stirred for 15 min. Then a solution of 2-(3-bromopropoxy)tetrahydro-2*H*-pyran (2.54 g, 11.4 mmol) in dry THF (10 mL) was added dropwise and the reaction mixture was allowed to warm to 23 °C slowly. After 40 h, the reaction mixture was diluted with water (5 mL) and extracted with Et_2O (4 × 25 mL). The combined organic extracts

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were washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 90:10) to give **35** (3.02 g, 81% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 4.61-4.56 (m, 1H), 4.54-4.45 (m, 1H), 3.92-3.76 (m, 2H), 3.55-3.41 (m, 2H), 2.36-2.24 (m, 2H), 1.88-1.66 (m, 4H), 1.64-1.46 (m, 4H), 1.37 (d, *J* 6.4, 3H), 0.90 (s, 9H), 0.11 (d, *J* 3.9, 6H).

(2*S*)-7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]hept-3-yn-2-ol (**8**). To a flask containing *tert*-butyldimethyl({(2*S*)-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]hept-3-yn-2-yl}oxy)silane (**35**, 3.59 g, 11 mmol) in dry THF (70 mL) was added a solution of Bu_4NF (1.0 M in THF, 22 mL, 22 mmol) and the reaction mixture was stirred at 23 °C for 2.5 h. Ice (15 mL) and Et_2O (30 mL) were added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 40:60) to give **8** (2.15 g, 92% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 4.59 (dd, *J* 4.4, 2.5, 1H), 4.50 (qt, *J* 6.6, 1.8, 1H), 3.91-3.77 (m, 2H), 3.55-3.42 (m, 2H), 2.32 (td, *J* 7.1, 1.8, 2H), 1.89-1.65 (m, 5H), 1.64-1.46 (m, 4H), 1.42 (d, *J* 6.6, 3H).

(2*S*,*E*)-7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]hept-3-en-2-ol (**9$_E$**). To a flask containing (2*S*)-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]hept-3-yn-2-ol (**8**, 2.12 g, 10 mmol) in dry THF (140 mL) was added dropwise at 0 °C a solution of sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al, 3.5 M in toluene, 5.7 mL, 20 mmol) and the reaction mixture was stirred at 0 °C for 15 min and then at 65 °C for 1 h. After cooling, ice (30 mL) and Et_2O (30 mL) were added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 80:20 to 25:75) to give **9$_E$** (1.99 g, 93% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 5.70-5.60 (m, 1H), 5.58-5.49 (m, 1H), 4.60-4.54 (m, 1H), 4.26 (q, *J* 6.4, 1H), 3.91-3.82 (m, 1H), 3.78-3.69 (m, 1H), 3.54-3.45 (m, 1H), 3.43-3.34 (m, 1H), 2.18-2.07 (m, 2H), 1.89-1.77 (m, 1H), 1.76-1.63 (m, 3H), 1.63-1.46 (m, 5H), 1.25 (d, *J* 6.4, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 134.5(7), 134.5(4), 130.3(1), 130.2(7), 98.9, 68.9, 66.8(5), 66.8(3), 62.3, 30.7, 29.1, 28.7(9), 28.7(6), 25.4, 23.4, 19.6.

2-{[(*S*,*E*)-6-(Benzyloxy)hept-4-en-1-yl]oxy}tetrahydro-2*H*-pyran (**36$_E$**). To a flask containing a suspension of NaH (60% dispersion in oil, 360 mg, 9 mmol) in dry DMF (12 mL) was added dropwise at 0 °C a solution of (2*S*,*E*)-7-[(tetrahydro-2H-pyran-2-yl)oxy]hept-3-en-2-ol **9$_E$** (2.14 g, 10 mmol) in dry DMF (8 mL) and the reaction mixture was stirred for 1 h. Benzyl bromide (1.54 g, 1.05 mL, 9 mmol) was added dropwise and the solution was stirred at 0 °C for 30 min and then at 23 °C for 24 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (5 mL) and Et_2O (150 mL) and the layers were separated. The organic layer was washed with H_2O (3 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude products was purified by column chromatography (pentane:Et_2O 90:10 to 40:60) to give **36$_E$** (1.37 g, 45% yield) and starting **9$_E$** (1.05 g, 49% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.36-7.30 (m, 4H), 7.30-7.22 (m, 1H), 5.64 (dt, *J* 15.3, 6.6, 1H), 5.42 (ddt, *J* 15.3, 7.7, 1.4, 1H), 4.60-4.56 (m, 1H), 4.55 (d, *J* 11.9, 1H), 4.36 (d, *J* 11.9, 1H), 3.93-3.82 (m, 2H), 3.81-3.72 (m, 1H), 3.54-3.46 (m, 1H), 3.45-3.36 (m, 1H), 2.23-2.10 (m, 2H), 1.90-1.77 (m, 1H), 1.76-1.66 (m, 3H), 1.64-1.46 (m, 4H), 1.27 (d, *J* 6.4, 3H).

(*S*,*E*)-6-(Benzyloxy)hept-4-en-1-ol (**37$_E$**). To a flask containing 2-{[(*S,E*)-6-(benzyloxy)hept-4-en-1-yl]oxy}tetrahydro-2H-pyran (**36$_E$**, 1.28 g, 4.2 mmol) in dry MeOH (10 mL) was added PPTS (53 mg, 0.21 mmol) and the reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was diluted with Et_2O (125 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL), H_2O (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 50:50) to give **37$_E$** (854 mg, 92% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ

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7.37-7.30 (m, 4H), 7.30-7.23 (m, 1H), 5.64 (dt, *J* 15.3, 6.4, 1H), 5.44 (ddt, *J* 15.3, 7.8, 1.4, 1H), 4.55 (d, *J* 11.9, 1H), 4.37 (d, *J* 12.1, 1H), 3.93-3.84 (m, 1H), 3.67 (t, *J* 6.6, 2H), 2.21-2.11 (m, 2H), 1.73-1.63 (m, 2H), 1.41 (s, 1H), 1.27 (d, *J* 6.4, 3H).

(*S*,*E*)-{[(7-Bromohept-3-en-2-yl)oxy]methyl}benzene (**10$_E$**). In a flask containing (*S*,*E*)-6-(benzyloxy)hept-4-en-1-ol **37$_E$** (400 mg, 1.82 mmol) and CBr_4 (1.21 g, 3.64 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise at 0 °C a solution of PPh_3 (954 mg, 3.64 mmol) in dry CH_2Cl_2 (5 mL) and the reaction mixture was stirred at 23 °C for 16 h. The reaction mixture was diluted with Et_2O (60 mL) and washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was triturated in pentane, filtered and the solvent removed under reduced pressure in order to remove most of the residual PPh_3 and its oxide. The crude product was purified by column chromatography (pentane:Et_2O 95:5 to 90:10) to give **10$_E$** (490 mg, 95% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.37-7.31 (m, 4H), 7.30-7.23 (m, 1H), 5.59 (dt, *J* 15.3, 6.4, 1H), 5.47 (ddt, *J* 15.3, 7.6, 1.1, 1H), 4.55 (d, *J* 11.9, 1H), 4.37 (d, *J* 12.1, 1H), 3.94-3.84 (m, 1H), 3.42 (t, *J* 6.6, 2H), 2.27-2.19 (m, 2H), 2.02-1.91 (m, 2H), 1.28 (d, *J* 6.4, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 138.8,133.6, 130.6, 128.3, 127.6, 127.4, 75.6, 69.8, 33.1, 32.0, 30.5, 21.7.

[(8*S*,*E*)-8-(Benzyloxy)-2-phenylnon-6-en-2-yl](methyl)selane (**1c$_E$**). To a flask containing (1-phenylethane-1,1-diyl)bis(methylselane) (350 mg, 1.2 mmol) in dry THF (4.3 mL) was added dropwise at -78 °C a solution of *n*-BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) and the reaction mixture was stirred for 40 min (yellow solution of **32**). A solution of (*S,E*)-{[(7-chlorohept-3-en-2-yl)oxy]methyl}benzene **10$_E$** (283 mg, 1 mmol) in dry THF (1.7 mL) was added dropwise and the reaction mixture stirred at -78 °C for 10 min (discoloration). MeOH (1 mL) was added, the reaction mixture was warm to 23 °C, diluted with Et_2O (60 mL) and washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (pentane:Et_2O 95:5) to give **1c$_E$** (384 mg, 96% yield). ^{1}H NMR (400 MHz, 21 °C, $CDCl_3$): δ 7.51-7.41 (m, 2H), 7.39-7.22 (m, 7H), 7.21-7.15 (m, 1H), 5.54 (dt, *J* 15.3, 6.6, 1H), 5.35 (dd, *J* 15.3, 7.8, 1H), 4.54 (d, *J* 11.9, 1H), 4.35 (dd, *J* 11.9, 1.6, 1H), 3.91-3.81 (m, 1H), 2.29-2.17 (m, 1H), 2.09-1.94 (m, 3H), 1.85 (s, 3H), 1.70 (s, 3H), 1.51-1.36 (m, 1H), 1.32-1.14 (m, 1H), 1.26 (d, *J* 6.2, 3H); ^{13}C NMR (100 MHz, 21 °C, $CDCl_3$): δ 145.2, 138.9, 132.5, 132.4, 128.3, 128.0, 127.6, 127.3, 126.8, 126.2, 75.7, 69.6, 46.6, 42.4, 32.4, 26.2, 24.6, 21.7, 3.3; IR (film): 2926, 1495, 1445, 1374, 1145, 1068, 1028, 970, 902, 733, 695, 654 cm^{-1}.

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30. (1*S*)-Camphanic chloride, Aldrich catalog number 226173, $[\alpha]_D^{23}$ = -18° (c = 2 in CCl_4).
31. X-ray measurements were performed on a Gemini Ultra R system (4-circle kappa platform, Ruby CCD detector) using Mo K irradiation (λ = 0.71073 Å). Structures were solved by direct methods with SHELS-97 program and then refined on F^2 using SHELXL-97 software, CCDC quotation refers to the crystal structures related to **13_1**-**13_4** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers below each structure.
32. Jeol JNM EX-400 spectrometer. The coupling constants between the two vinylic hydrogens are *J* 15.3 (**$4c_{E1}$**, **$4c_{E3}$**) and 15.1 (**$4c_{E2}$**, **$4b_{E4}$**) for the *E*-stereoisomers and *J* 11.7 for the *Z*-stereoisomer (**$4c_{Z1}$**), $CDCl_3$.
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